PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 9/00

A2

(11) International Publication Number: WO 99/66028

(43) International Publication Date: 23 December 1999 (23.12.99)

(21) International Application Number: PCT/EP99/04171

(22) International Filing Date: 16 June 1999 (16.06.99)

(30) Priority Data:

09/099,504	18 June 1998 (18.06.98)	US
60/101,631	24 September 1998 (24.09.98)	US
60/118,906	5 February 1999 (05.02.99)	US

(71) Applicant *(for all designated States except AT US)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).

(71) Applicant *(for AT only)*: NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SCHUPP, Thomas [CH/CH]; Fröschmattweg 5, CH-4313 Möhlin (CH). LIGON, James, Madison [US/US]; 3616 South Pointe Drive, Apex, NC 27502 (US). MOLNAR, Istvan [HU/US]; 4004 Branchwood Drive, Durham, NC 27705 (US). ZIRKLE, Ross [US/US]; 6532 Wynbrook Way, Raleigh, NC 27612 (US). GÖRLACH, Jörn [DE/US]; 3907 King Charles Road, Durham, NC 27707 (US). CYR, Devon [US/US]; 413 Vuncannon Drive, Fuquay-Varina, NC 27526 (US).

(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: GENES FOR THE BIOSYNTHESIS OF EPOTHILONES

(57) Abstract

Nucleic acid molecules are isolated from *Sorangium cellulosum* that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

GENES FOR THE BIOSYNTHESIS OF EPOTHILONES

FIELD OF THE INVENTION

The present invention relates generally to polyketides and genes for their synthesis. In particular, the present invention relates to the isolation and characterization of novel polyketide synthase and nonribosomal peptide synthetase genes from *Sorangium cellulosum* that are necessary for the biosynthesis of epothilones A and B.

BACKGROUND OF THE INVENTION

Polyketides are compounds synthesized from two-carbon building blocks, the β-carbon of which always carries a keto group, thus the name polyketide. These compounds include many important antibiotics, immunosuppressants, cancer chemotherapeutic agents, and other compounds possessing a broad range of biological properties. The tremendous structural diversity derives from the different lengths of the polyketide chain, the different side-chains introduced (either as part of the two-carbon building blocks or after the polyketide backbone is formed), and the stereochemistry of such groups. The keto groups may also be reduced to hydroxyls, enoyls, or removed altogether. Each round of two-carbon addition is carried out by a complex of enzymes called the polyketide synthase (PKS) in a manner similar to fatty acid biosynthesis.

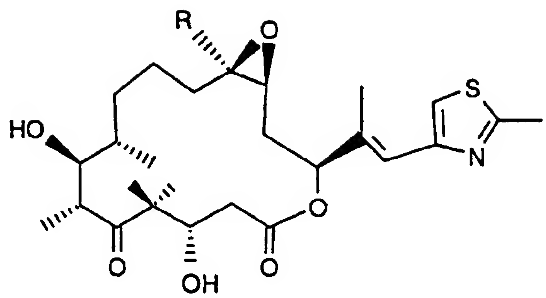
The biosynthetic genes for an increasing number of polyketides have been isolated and sequenced. For example, *see* U.S. Patent Nos. 5,639,949, 5,693,774, and 5,716,849, all of which are incorporated herein by reference, which describe genes for the biosynthesis of soraphen. *See also*, Schupp *et al.*, *FEMS Microbiology Letters* 159: 201-207 (1998) and WO 98/07868, which describe genes for the biosynthesis of rifamycin, and U.S. Patent No. 5,876,991, which describes genes for the biosynthesis of tylactone, all of which are incorporated herein by reference. The encoded proteins generally fall into two types: type I and type II. Type I proteins are polyfunctional, with several catalytic domains carrying out different enzymatic steps covalently linked together (e.g. PKS for erythromycin, soraphen, rifamycin, and avermectin (MacNeil *et al.*, in *Industrial Microorganisms: Basic and Applied Molecular Genetics*, (ed.: Baltz *et al.*), American Society for Microbiology, Washington D. C.

pp. 245-256 (1993)); whereas type II proteins are monofunctional (Hutchinson *et al.*, in *Industrial Microorganisms: Basic and Applied Molecular Genetics*, (ed.: Baltz *et al.*), American Society for Microbiology, Washington D. C. pp. 203-216 (1993)).

For the simpler polyketides such as actinorhodin (produced by *Streptomyces coelicolor*), the several rounds of two-carbon additions are carried out iteratively on PKS enzymes encoded by one set of PKS genes. In contrast, synthesis of the more complicated compounds such as erythromycin and soraphen involves PKS enzymes that are organized into modules, whereby each module carries out one round of two-carbon addition (for review, see Hopwood *et al.*, in *Industrial Microorganisms: Basic and Applied Molecular Genetics*, (ed.: Baltz *et al.*), American Society for Microbiology, Washington D. C., pp. 267-275 (1993)).

Complex polyketides and secondary metabolites in general may contain substructures that are derived from amino acids instead of simple carboxylic acids. Incorporations of these building blocks are accomplished by non-ribosomal polypeptide synthetases (NRPSs). NRPSs are multienzymes that are organized in modules. Each module is responsible for the addition (and the additional processing, if required) of one amino acid building block. NRPSs activate amino acids by forming aminoacyl-adenylates, and capture the activated amino acids on thiol groups of phophopantheteinyl prosthetic groups on peptidyl carrier protein domains. Further, NRPSs modify the amino acids by epimerization, N-methylation, or cyclization if necessary, and catalyse the formation of peptide bonds between the enzyme-bound amino acids. NRPSs are responsible for the biosynthesis of peptide secondary metabolites like cyclosporin, could provide polyketide chain terminator units as in rapamycin, or form mixed systems with PKSs as in yersiniabactin biosynthesis.

Epothilones A and B are 16-membered macrocyclic polyketides with an acylcysteine-derived starter unit that are produced by the bacterium *Sorangium cellulosum* strain So ce90 (Gerth *et al.*, *J. Antibiotics* 49: 560-563 (1996), incorporated herein by reference). The structure of epothilone A and B wherein R signifies hydrogen (epothilone A) or methyl (epothilone B) is:



The epothilones have a narrow antifungal spectrum and especially show a high cytotoxicity in animal cell cultures (*see*, Höfle *et al.*, Patent DE 4138042 (1993), incorporated herein by reference). Of significant importance, epothilones mimic the biological effects of taxol, both *in vivo* and in cultured cells (Bollag *et al.*, *Cancer Research* 55: 2325-2333 (1995), incorporated herein by reference). Taxol and taxotere, which stabilize cellular microtubules, are cancer chemotherapeutic agents with significant activity against various human solid tumors (Rowinsky *et al.*, *J. Natl. Cancer Inst.* 83: 1778-1781 (1991)). Competition studies have revealed that epothilones act as competitive inhibitors of taxol binding to microtubules, consistent with the interpretation that they share the same microtubule-binding site and possess a similar microtubule affinity as taxol. However, epothilones enjoy a significant advantage over taxol in that epothilones exhibit a much lower drop in potency compared to taxol against a multiple drug-resistant cell line (Bollag *et al.* (1995)). Furthermore, epothilones are considerably less efficiently exported from the cells by P-glycoprotein than is taxol (Gerth *et al.* (1996)). In addition, several epothilone analogs have been synthesized that have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymerization and stabilization of microtubules (WO 98/25929, incorporated herein by reference).

Despite the promise shown by the epothilones as anticancer agents, problems pertaining to the production of these compounds presently limit their commercial potential. The compounds are too complex for industrial-scale chemical synthesis and so must be produced by fermentation. Techniques for the genetic manipulation of myxobacteria such as *Sorangium cellulosum* are described in U.S. Patent No. 5,686,295, incorporated herein by reference. However, *Sorangium cellulosum* is notoriously difficult to ferment and production levels of epothilones are therefore low. Recombinant production of epothilones in heterologous hosts that are more amenable to fermentation could solve current production problems. However, the genes that encode the polypeptides responsible for epothilone bio-

synthesis have heretofore not been isolated. Furthermore, the strain that produces epothilones, i.e. So ce90, also produces at least one additional polyketide, spirangien, which would be expected to greatly complicate the isolation of the genes particularly responsible for epothilone biosynthesis.

Therefore, in view of the foregoing, one object of the present invention is to isolate the genes that are involved in the synthesis of epothilones, particularly the genes that are involved in the synthesis of epothilones A and B in myxobacteria of the Sorangium/-Polyangium group, i.e., *Sorangium cellulosum* strain So ce90. A further object of the invention is to provide a method for the recombinant production of epothilones for application in anticancer formulations.

SUMMARY OF THE INVENTION

In furtherance of the aforementioned and other objects, the present invention unexpectedly overcomes the difficulties set forth above to provide for the first time a nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of epothilone. In a preferred embodiment, the nucleotide sequence is isolated from a species belonging to *Myxobacteria*, most preferably *Sorangium cellulosum*.

In another preferred embodiment, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of an epothilone, wherein said polypeptide comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: SEQ ID NO:2, amino acids 11-437 of SEQ ID NO:2, amino acids 543-864 of SEQ ID NO:2, amino acids 974-1273 of SEQ ID NO:2, amino acids 1314-1385 of SEQ ID NO:2, SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, amino acids 1344-1351 of SEQ ID NO:3, SEQ ID NO:4, amino acids 7-432 of SEQ ID NO:4, amino acids 539-859 of SEQ ID NO:4, amino acids 869-1037 of SEQ ID NO:4, amino acids 1439-1684 of SEQ ID NO:4, amino acids 1722-1792 of SEQ ID

NO:4, SEQ ID NO:5, amino acids 39-457 of SEQ ID NO:5, amino acids 563-884 of SEQ ID NO:5, amino acids 1147-1399 of SEQ ID NO:5, amino acids 1434-1506 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 3886-4048 of SEQ ID NO:5, amino acids 4433-4719 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, SEQ ID NO:6, amino acids 35-454 of SEQ ID NO:6, amino acids 561-881 of SEQ ID NO:6, amino acids 1143-1393 of SEQ ID NO:6, amino acids 1430-1503 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, amino acids 2053-2373 of SEQ ID NO:6, amino acids 2383-2551 of SEQ ID NO:6, amino acids 2671-3045 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, SEQ ID NO:7, amino acids 32-450 of SEQ ID NO:7, amino acids 556-877 of SEQ ID NO:7, amino acids 887-1051 of SEQ ID NO:7, amino acids 1478-1790 of SEQ ID NO:7, amino acids 1810-2055 of SEQ ID NO:7, amino acids 2093-2164 of SEQ ID NO:7, amino acids 2165-2439 of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:22.

In a more preferred embodiment, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of an epothilone, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:2, amino acids 11-437 of SEQ ID NO:2, amino acids 543-864 of SEQ ID NO:2, amino acids 974-1273 of SEQ ID NO:2, amino acids 1314-1385 of SEQ ID NO:2, SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, amino acids 1344-1351 of SEQ ID NO:3, SEQ ID NO:4, amino acids 7-432 of SEQ ID NO:4, amino acids 539-859 of SEQ ID NO:4, amino acids 869-1037 of SEQ ID NO:4, amino acids 1439-1684

of SEQ ID NO:4, amino acids 1722-1792 of SEQ ID NO:4, SEQ ID NO:5, amino acids 39-457 of SEQ ID NO:5, amino acids 563-884 of SEQ ID NO:5, amino acids 1147-1399 of SEQ ID NO:5, amino acids 1434-1506 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 3886-4048 of SEQ ID NO:5, amino acids 4433-4719 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, SEQ ID NO:6, amino acids 35-454 of SEQ ID NO:6, amino acids 561-881 of SEQ ID NO:6, amino acids 1143-1393 of SEQ ID NO:6, amino acids 1430-1503 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, amino acids 2053-2373 of SEQ ID NO:6, amino acids 2383-2551 of SEQ ID NO:6, amino acids 2671-3045 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, SEQ ID NO:7, amino acids 32-450 of SEQ ID NO:7, amino acids 556-877 of SEQ ID NO:7, amino acids 887-1051 of SEQ ID NO:7, amino acids 1478-1790 of SEQ ID NO:7, amino acids 1810-2055 of SEQ ID NO:7, amino acids 2093-2164 of SEQ ID NO:7, amino acids 2165-2439 of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:22.

In yet another preferred embodiment, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of an epothilone, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: the complement of nucleotides 1900-3171 of SEQ ID NO:1, nucleotides 3415-5556 of SEQ ID NO:1, nucleotides 7610-11875 of SEQ ID NO:1, nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1,

nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, nucleotides 15901-15924 of SEQ ID NO:1, nucleotides 16251-21749 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 21746-43519 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 43524-54920 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, nucleotides 51534-52657 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, nucleotides 54935-62254 of SEQ ID NO:1, nucleotides 55028-56284 of SEQ ID NO:1, nucleotides 56600-57565 of SEQ ID NO:1, nucleotides 57593-58087 of SEQ ID NO:1, nucleotides 59366-60304 of SEQ ID NO:1, nucleotides 60362-61099 of SEQ ID NO:1, nucleotides 61211-61426 of SEQ ID NO:1, nucleotides 61427-62254 of SEQ ID NO:1, nucleotides 62369-63628 of SEQ ID NO:1, nucleotides 67334-68251 of SEQ ID NO:1, and nucleotides 1-68750 SEQ ID NO:1.

In an especially preferred embodiment, the present invention provides a nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of an epothilone, wherein said nucleotide sequence is selected from the group consisting of: the complement of nucleotides 1900-3171 of SEQ ID NO:1, nucleotides 3415-5556 of SEQ ID NO:1, nucleotides 7610-11875 of SEQ ID NO:1, nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 11872-16104 of

SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, nucleotides 15901-15924 of SEQ ID NO:1, nucleotides 16251-21749 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 21746-43519 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 43524-54920 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, nucleotides 51534-52657 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, nucleotides 54935-62254 of SEQ ID NO:1, nucleotides 55028-56284 of SEQ ID NO:1, nucleotides 56600-57565 of SEQ ID NO:1, nucleotides 57593-58087 of SEQ ID NO:1, nucleotides 59366-60304 of SEQ ID NO:1, nucleotides 60362-61099 of SEQ ID NO:1, nucleotides 61211-61426 of SEQ ID NO:1, nucleotides 61427-62254 of SEQ ID NO:1, nucleotides 62369-63628 of SEQ ID NO:1, nucleotides 67334-68251 of SEQ ID NO:1, and nucleotides 1-68750 SEQ ID NO:1.

In yet another preferred embodiment, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of an epothilone, wherein said nucleotide sequence comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: the complement of nucleotides 1900-3171 of SEQ ID NO:1, nucleotides 3415-5556 of SEQ ID NO:1, nucleotides 7610-11875 of SEQ ID NO:1, nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, nucleotides 15901-15924 of SEQ ID NO:1, nucleotides 16251-21749 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 21746-43519 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 43524-54920 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID

NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, nucleotides 51534-52657 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, nucleotides 54935-62254 of SEQ ID NO:1, nucleotides 55028-56284 of SEQ ID NO:1, nucleotides 56600-57565 of SEQ ID NO:1, nucleotides 57593-58087 of SEQ ID NO:1, nucleotides 59366-60304 of SEQ ID NO:1, nucleotides 60362-61099 of SEQ ID NO:1, nucleotides 61211-61426 of SEQ ID NO:1, nucleotides 61427-62254 of SEQ ID NO:1, nucleotides 62369-63628 of SEQ ID NO:1, nucleotides 67334-68251 of SEQ ID NO:1, and nucleotides 1-68750 SEQ ID NO:1.

The present invention also provides a chimeric gene comprising a heterologous promoter sequence operatively linked to a nucleic acid molecule of the invention. Further, the present invention provides a recombinant vector comprising such a chimeric gene, wherein the vector is capable of being stably transformed into a host cell. Still further, the present invention provides a recombinant host cell comprising such a chimeric gene, wherein the host cell is capable of expressing the nucleotide sequence that encodes at least one polypeptide necessary for the biosynthesis of an epothilone. In a preferred embodiment, the recombinant host cell is a bacterium belonging to the order *Actinomycetales*, and in a more preferred embodiment the recombinant host cell is a strain of *Streptomyces*. In other embodiments, the recombinant host cell is any other bacterium amenable to fermentation, such as a pseudomonad or *E. coli*. Even further, the present invention provides a Bac clone comprising a nucleic acid molecule of the invention, preferably Bac clone pEPO15.

In another aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes an epothilone synthase domain.

According to one embodiment, the epothilone synthase domain is a β-ketoacyl-synthase (KS) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7. According to this embodiment, said KS domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids

3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, and nucleotides 55028-56284 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, and nucleotides 55028-56284 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, and nucleotides 55028-56284 of SEQ ID NO:1.

According to another embodiment, the epothilone synthase domain is an acyltransferase (AT) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7. According to this embodiment, said AT domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino

acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, and nucleotides 56600-57565 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, and nucleotides 56600-57565 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, and nucleotides 56600-57565 of SEQ ID NO:1.

According to still another embodiment, the epothilone synthase domain is an enoyl reductase (ER) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7. According to this embodiment, said ER domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 10529-11428 of

SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, and nucleotides 59366-60304 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, and nucleotides 59366-60304 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, and nucleotides 59366-60304 of SEQ ID NO:1.

According to another embodiment, the epothilone synthase domain is an acyl carrier protein (ACP) domain, wherein said polypeptide comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7. According to this embodiment, said ACP domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, and nucleotides 61211-61426 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40,

45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, and nucleotides 61211-61426 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, and nucleotides 61211-61426 of SEQ ID NO:1.

According to another embodiment, the epothilone synthase domain is a dehydratase (DH) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7. According to this embodiment, said DH domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, and nucleotides 57593-58087 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, and nucleotides 57593-58087 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 18855-19361 of SEQ ID NO:1,

nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, and nucleotides 57593-58087 of SEQ ID NO:1.

According to yet another embodiment, the epothilone synthase domain is a β-keto-reductase (KR) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7. According to this embodiment, said KR domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, and nucleotides 60362-61099 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, and nucleotides 60362-61099 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, and nucleotides 60362-61099 of SEQ ID NO:1.

According to an additional embodiment, the epothilone synthase domain is a methyltransferase (MT) domain comprising an amino acid sequence substantially similar to amino acids 2671-3045 of SEQ ID NO:6. According to this embodiment, said MT domain preferably comprises amino acids 2671-3045 of SEQ ID NO:6. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to nucleotides 51534-52657 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of nucleotides 51534-52657 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is nucleotides 51534-52657 of SEQ ID NO:1.

According to another embodiment, the epothilone synthase domain is a thioesterase (TE) domain comprising an amino acid sequence substantially similar to amino acids 2165-2439 of SEQ ID NO:7. According to this embodiment, said TE domain preferably comprises amino acids 2165-2439 of SEQ ID NO:7. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to nucleotides 61427-62254 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of nucleotides 61427-62254 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is nucleotides 61427-62254 of SEQ ID NO:1.

In still another aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a non-ribosomal peptide synthetase, wherein said non-ribosomal peptide synthetase comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, and amino acids 1344-1351 of SEQ ID NO:3. According to this

embodiment, said non-ribosomal peptide synthetase preferably comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, and amino acids 1344-1351 of SEQ ID NO:3. Also, according to this embodiment, said nucleotide sequence preferably is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, and nucleotides 15901-15924 of SEQ ID NO:1. According to this embodiment, said nucleotide sequence more preferably comprises a consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair nucleotide portion identical in sequence to a respective consecutive 20, 25, 30, 35, 40, 45, or 50 (preferably 20) base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, and nucleotides 15901-15924 of SEQ ID NO:1. In addition, according to this embodiment, said nucleotide sequence most preferably is selected from the group consisting of: nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-

12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, and nucleotides 15901-15924 of SEQ ID NO:1.

The present invention further provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:2-23.

In accordance with another aspect, the present invention also provides methods for the recombinant production of polyketides such as epothilones in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer. A specific advantage of these production methods is the chirality of the molecules produced; production in transgenic organisms avoids the generation of populations of racemic mixtures, within which some enantiomers may have reduced activity. In particular, the present invention provides a method for heterologous expression of epothilone in a recombinant host, comprising: (a) introducing into a host a chimeric gene comprising a heterologous promoter sequence operatively linked to a nucleic acid molecule of the invention that comprises a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of epothilone; and (b) growing the host in conditions that allow biosynthesis of epothilone in the host. The present invention also provides a method for producing epothilone, comprising: (a) expressing epothilone in a recombinant host by the aforementioned method; and (b) extracting epothilone from the recombinant host.

According to still another aspect, the present invention provides an isolated polypeptide comprising an amino acid sequence that consists of an epothilone synthase domain.

According to one embodiment, the epothilone synthase domain is a β-ketoacyl-synthase (KS) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7. According to this embodiment,

said KS domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7.

According to another embodiment, the epothilone synthase domain is an acyltransferase (AT) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7. According to this embodiment, said AT domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7.

According to still another embodiment, the epothilone synthase domain is an enoyl reductase (ER) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7. According to this embodiment, said ER domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7.

According to another embodiment, the epothilone synthase domain is an acyl carrier protein (ACP) domain, wherein said polypeptide comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of

SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7. According to this embodiment, said ACP domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7.

According to another embodiment, the epothilone synthase domain is a dehydratase (DH) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7. According to this embodiment, said DH domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7.

According to yet another embodiment, the epothilone synthase domain is a β-ketoreductase (KR) domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7. According to this embodiment, said KR domain preferably comprises an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7.

According to an additional embodiment, the epothilone synthase domain is a methyltransferase (MT) domain comprising an amino acid sequence substantially similar to amino acids 2671-3045 of SEQ ID NO:6. According to this embodiment, said MT domain preferably comprises amino acids 2671-3045 of SEQ ID NO:6.

According to another embodiment, the epothilone synthase domain is a thioesterase (TE) domain comprising an amino acid sequence substantially similar to amino acids 2165-2439 of SEQ ID NO:7. According to this embodiment, said TE domain preferably comprises amino acids 2165-2439 of SEQ ID NO:7.

Other aspects and advantages of the present invention will become apparent to those skilled in the art from a study of the following description of the invention and non-limiting examples.

DEFINITIONS

In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

Associated With / Operatively Linked: Refers to two DNA sequences that are related physically or functionally. For example, a promoter or regulatory DNA sequence is said to be "associated with" a DNA sequence that codes for an RNA or a protein if the two sequences are operatively linked, or situated such that the regulator DNA sequence will affect the expression level of the coding or structural DNA sequence.

Chimeric Gene: A recombinant DNA sequence in which a promoter or regulatory DNA sequence is operatively linked to, or associated with, a DNA sequence that codes for an mRNA or which is expressed as a protein, such that the regulator DNA sequence is able to regulate transcription or expression of the associated DNA sequence. The regulator DNA sequence of the chimeric gene is not normally operatively linked to the associated DNA sequence as found in nature.

Coding DNA Sequence: A DNA sequence that is translated in an organism to produce a protein.

Domain: That part of a polyketide synthase necessary for a given distinct activity. Examples include acyl carrier protein (ACP), β-ketosynthase (KS), acyltransferase (AT), β-ketoreductase (KR), dehydratase (DH), enoylreductase (ER), and thioesterase (TE) domains.

Epothilones: 16-membered macrocyclic polyketides naturally produced by the bacterium *Sorangium cellulosum* strain So ce90, which mimic the biological effects of taxol. In this application, "epothilone" refers to the class of polyketides that includes epothilone A and epothilone B, as well as analogs thereof such as those described in WO 98/25929.

Epothilone Synthase: A polyketide synthase responsible for the biosynthesis of epothilone.

Gene: A defined region that is located within a genome and that, besides the aforementioned coding DNA sequence, comprises other, primarily regulatory, DNA sequences responsible for the control of the expression, that is to say the transcription and translation, of the coding portion.

Heterologous DNA Sequence: A DNA sequence not naturally associated with a host cell into which it is introduced, including non-naturally occurring multiple copies of a naturally occurring DNA sequence.

Homologous DNA Sequence: A DNA sequence naturally associated with a host cell into which it is introduced.

Homologous Recombination: Reciprocal exchange of DNA fragments between homologous DNA molecules.

Isolated: In the context of the present invention, an isolated nucleic acid molecule or an isolated enzyme is a nucleic acid molecule or enzyme that, by the hand of man, exists apart from its native environment and is therefore not a product of nature. An isolated nucleic acid molecule or enzyme may exist in a purified form or may exist in a non-native environment such as, for example, a recombinant host cell.

Module: A genetic element encoding all of the distinct activities required in a single round of polyketide biosynthesis, i.e., one condensation step and all the β-carbonyl processing steps associated therewith. Each module encodes an ACP, a KS, and an AT activity to accomplish the condensation portion of the biosynthesis, and selected post-condensation activities to effect the β-carbonyl processing.

NRPS: A non-ribosomal polypeptide synthetase, which is a complex of enzymatic activities responsible for the incorporation of amino acids into secondary metabolites including, for example, amino acid adenylation, epimerization, N-methylation, cyclization, peptidyl carrier protein, and condensation domains. A functional NRPS is one that catalyzes the incorporation of an amino acid into a secondary metabolite.

NRPS gene: One or more genes encoding NRPSs for producing functional secondary metabolites, e.g., epothilones A and B, when under the direction of one or more compatible control elements.

Nucleic Acid Molecule: A linear segment of single- or double-stranded DNA or RNA that can be isolated from any source. In the context of the present invention, the nucleic acid molecule is preferably a segment of DNA.

ORF: Open Reading Frame.

PKS: A polyketide synthase, which is a complex of enzymatic activities (domains) responsible for the biosynthesis of polyketides including, for example, ketoreductase, dehydratase, acyl carrier protein, enoylreductase, ketoacyl ACP synthase, and acyltransferase. A functional PKS is one that catalyzes the synthesis of a polyketide.

PKS Genes: One or more genes encoding various polypeptides required for producing functional polyketides, e.g., epothilones A and B, when under the direction of one or more compatible control elements.

Substantially Similar: With respect to nucleic acids, a nucleic acid molecule that has at least 60 percent sequence identity with a reference nucleic acid molecule. In a preferred embodiment, a substantially similar DNA sequence is at least 80% identical to a reference DNA sequence; in a more preferred embodiment, a substantially similar DNA sequence is at least 90% identical to a reference DNA sequence; and in a most preferred embodiment, a substantially similar DNA sequence is at least 95% identical to a reference DNA sequence. A substantially similar DNA sequence preferably encodes a protein or peptide having substantially the same activity as the protein or peptide encoded by the reference DNA sequence. A substantially similar nucleotide sequence typically hybridizes to a reference nucleic acid molecule, or fragments thereof, under the following conditions: hybridization at 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$ pH 7.0, 1 mM EDTA at 50°C; wash with 2X SSC, 1% SDS, at 50°C. With respect to proteins or peptides, a substantially similar amino acid sequence is an amino acid sequence that is at least 90% identical to the amino acid sequence of a reference protein or peptide and has substantially the same activity as the reference protein or peptide.

Transformation: A process for introducing heterologous nucleic acid into a host cell or organism.

Transformed / Transgenic / Recombinant: Refers to a host organism such as a bacterium into which a heterologous nucleic acid molecule has been introduced. The nucleic acid molecule can be stably integrated into the genome of the host or the nucleic acid molecule can also be present as an extrachromosomal molecule. Such an extrachromosomal molecule can be auto-replicating. Transformed cells, tissues, or plants are understood to

encompass not only the end product of a transformation process, but also transgenic progeny thereof. A "non-transformed", "non-transgenic", or "non-recombinant" host refers to a wild-type organism, i.e., a bacterium, which does not contain the heterologous nucleic acid molecule.

Nucleotides are indicated by their bases by the following standard abbreviations: adenine (A), cytosine (C), thymine (T), and guanine (G). Amino acids are likewise indicated by the following standard abbreviations: alanine (ala; A), arginine (Arg; R), asparagine (Asn; N), aspartic acid (Asp; D), cysteine (Cys; C), glutamine (Gln; Q), glutamic acid (Glu; E), glycine (Gly; G), histidine (His; H), isoleucine (Ile; I), leucine (Leu; L), lysine (lys; K), methionine (Met; M), phenylalanine (Phe; F), proline (Pro; P), serine (Ser; S), threonine (Thr; T), tryptophan (Trp; W), tyrosine (Tyr; Y), and valine (Val; V). Furthermore, (Xaa; X) represents any amino acid.

DESCRIPTION OF THE SEQUENCES IN THE SEQUENCE LISTING

SEQ ID NO:1 is the nucleotide sequence of a 68750 bp contig containing 22 open reading frames (ORFs), which comprises the epothilone biosynthesis genes.

SEQ ID NO:2 is the protein sequence of a type I polyketide synthase (EPOS A) encoded by *epo*A (nucleotides 7610-11875 of SEQ ID NO:1).

SEQ ID NO:3 is the protein sequence of a non-ribosomal peptide synthetase (EPOS P) encoded by *epo*P (nucleotides 11872-16104 of SEQ ID NO:1).

SEQ ID NO:4 is the protein sequence of a type I polyketide synthase (EPOS B) encoded by *epo*B (nucleotides 16251-21749 of SEQ ID NO:1).

SEQ ID NO:5 is the protein sequence of a type I polyketide synthase (EPOS C) encoded by *epo*C (nucleotides 21746-43519 of SEQ ID NO:1).

SEQ ID NO:6 is the protein sequence of a type I polyketide synthase (EPOS D) encoded by *epo*D (nucleotides 43524-54920 of SEQ ID NO:1).

SEQ ID NO:7 is the protein sequence of a type I polyketide synthase (EPOS E) encoded by *epo*E (nucleotides 54935-62254 of SEQ ID NO:1).

SEQ ID NO:8 is the protein sequence of a cytochrome P450 oxygenase homologue (EPOS F) encoded by *epo*F (nucleotides 62369-63628 of SEQ ID NO:1).

SEQ ID NO:9 is a partial protein sequence (partial Orf 1) encoded by *orf*1 (nucleotides 1-1826 of SEQ ID NO:1).

SEQ ID NO:10 is a protein sequence (Orf 2) encoded by *orf*2 (nucleotides 3171-1900 on the reverse complement strand of SEQ ID NO:1).

SEQ ID NO:11 is a protein sequence (Orf 3) encoded by *orf*3 (nucleotides 3415-5556 of SEQ ID NO:1).

SEQ ID NO:12 is a protein sequence (Orf 4) encoded by *orf*4 (nucleotides 5992-5612 on the reverse complement strand of SEQ ID NO:1).

SEQ ID NO:13 is a protein sequence (Orf 5) encoded by *orf*5 (nucleotides 6226-6675 of SEQ ID NO:1).

SEQ ID NO:14 is a protein sequence (Orf 6) encoded by *orf*6 (nucleotides 63779-64333 of SEQ ID NO:1).

SEQ ID NO:15 is a protein sequence (Orf 7) encoded by *orf*7 (nucleotides 64290-63853 on the reverse complement strand of SEQ ID NO:1).

SEQ ID NO:16 is a protein sequence (Orf 8) encoded by *orf*8 (nucleotides 64363-64920 of SEQ ID NO:1).

SEQ ID NO:17 is a protein sequence (Orf 9) encoded by *orf*9 (nucleotides 64727-64287 on the reverse complement strand of SEQ ID NO:1).

SEQ ID NO:18 is a protein sequence (Orf 10) encoded by *orf*10 (nucleotides 65063-65767 of SEQ ID NO:1).

SEQ ID NO:19 is a protein sequence (Orf 11) encoded by *orf*11 (nucleotides 65874-65008 on the reverse complement strand of SEQ ID NO:1).

SEQ ID NO:20 is a protein sequence (Orf 12) encoded by *orf*12 (nucleotides 66338-65871 on the reverse complement strand of SEQ ID NO:1).

SEQ ID NO:21 is a protein sequence (Orf 13) encoded by *orf*13 (nucleotides 66667-67137 of SEQ ID NO:1).

SEQ ID NO:22 is a protein sequence (Orf 14) encoded by *orf*14 (nucleotides 67334-68251 of SEQ ID NO:1).

SEQ ID NO:23 is a partial protein sequence (partial Orf 15) encoded by *orf*15 (nucleotides 68346-68750 of SEQ ID NO:1).

SEQ ID NO:24 is the universal reverse PCR primer sequence.

SEQ ID NO:25 is the universal forward PCR primer sequence.

SEQ ID NO:26 is the NH24 end "B" PCR primer sequence.

SEQ ID NO:27 is the NH2 end "A" PCR primer sequence.

SEQ ID NO:28 is the NH2 end "B" PCR primer sequence.

SEQ ID NO:29 is the pEPO15-NH6 end "B" PCR primer sequence.

SEQ ID NO:30 is the pEPO15-H2.7 end "A" PCR primer sequence.

DEPOSIT INFORMATION

The following material has been deposited with the Agricultural Research Service, Patent Culture Collection (NRRL), 1815 North University Street, Peoria, Illinois 61604, under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. All restrictions on the availability of the deposited material will be irrevocably removed upon the granting of a patent.

Deposited Material	Accession Number	Deposit Date
pEPO15	NRRL B-30033	June 11, 1998
pEPO32	NRRL B-30119	April 16, 1999

DETAILED DESCRIPTION OF THE INVENTION

The genes involved in the biosynthesis of epothilones can be isolated using the techniques according to the present invention. The preferable procedure for the isolation of epothilone biosynthesis genes requires the isolation of genomic DNA from an organism identified as producing epothilones A and B, and the transfer of the isolated DNA on a suitable plasmid or vector to a host organism that does not normally produce the polyketide, followed by the identification of transformed host colonies to which the epothilone-producing ability has been conferred. Using a technique such as λ::Tn5 transposon mutagenesis (de Bruijn & Lupski, *Gene* 27: 131-149 (1984)), the exact region of the transforming epothilone-conferring DNA can be more precisely defined. Alternatively or additionally, the transforming epothilone-conferring DNA can be cleaved into smaller fragments and the smallest that maintains the epothilone-conferring ability further characterized. Whereas the host organism lacking the ability to produce epothilone may be a different species from the organism from which the polyketide derives, a variation of this technique involves the transformation of host DNA into the same host that has had its epothilone-producing ability disrupted by mutagenesis. In this method, an epothilone-producing organism is mutated and non-epothilone-producing mutants are isolated. These are then complemented by genomic DNA isolated from the epothilone-producing parent strain.

A further example of a technique that can be used to isolate genes required for epothilone biosynthesis is the use of transposon mutagenesis to generate mutants of an epothilone-producing organism that, after mutagenesis, fails to produce the polyketide. Thus, the region of the host genome responsible for epothilone production is tagged by the transposon and can be recovered and used as a probe to isolate the native genes from the parent strain. PKS genes that are required for the synthesis of polyketides and that are similar to known PKS genes may be isolated by virtue of their sequence homology to the biosynthetic genes for which the sequence is known, such as those for the biosynthesis of rifamycin or soraphen. Techniques suitable for isolation by homology include standard library screening by DNA hybridization.

Preferred for use as a probe molecule is a DNA fragment that is obtainable from a gene or another DNA sequence that plays a part in the synthesis of a known polyketide. A preferred probe molecule comprises a 1.2 kb *Sma*I DNA fragment encoding the ketosynthase domain of the fourth module of the soraphen PKS (U.S. Patent No. 5,716,849), and a more preferred probe molecule comprises the β-ketoacyl synthase domains from the first and second modules of the rifamycin PKS (Schupp *et al.*, *FEMS Microbiology Letters* 159: 201-207 (1998)). These can be used to probe a gene library of an epothilone-producing microorganism to isolate the PKS genes responsible for epothilone biosynthesis.

Despite the well-known difficulties with PKS gene isolation in general and despite the difficulties expected to be encountered with the isolation of epothilone biosynthesis genes in particular, by using the methods described in the instant specification, biosynthetic genes for epothilones A and B can surprisingly be cloned from a microorganism that produces that polyketide. Using the methods of gene manipulation and recombinant production described in this specification, the cloned PKS genes can be modified and expressed in transgenic host organisms.

The isolated epothilone biosynthetic genes can be expressed in heterologous hosts to enable the production of the polyketide with greater efficiency than might be possible from native hosts. Techniques for these genetic manipulations are specific for the different available hosts and are known in the art. For example, heterologous genes can be expressed in *Streptomyces* and other actinomycetes using techniques such as those described in McDaniel *et al.*, *Science* 262: 1546-1550 (1993) and Kao *et al.*, *Science* 265: 509-512 (1994), both of which are incorporated herein by reference. *See also*, Rowe *et al.*, *Gene*

216: 215-223 (1998); Holmes *et al.*, *EMBO Journal* 12(8): 3183-3191 (1993) and Bibb *et al.*, *Gene* 38: 215-226 (1985), all of which are incorporated herein by reference.

Alternately, genes responsible for polyketide biosynthesis, i.e., epothilone biosynthetic genes, can also be expressed in other host organisms such as pseudomonads and *E. coli.* Techniques for these genetic manipulations are specific for the different available hosts and are known in the art. For example, PKS genes have been sucessfully expressed in *E. coli* using the pT7-7 vector, which uses the T7 promoter. *See*, Tabor *et al.*, *Proc. Natl. Acad. Sci. USA* 82: 1074-1078 (1985), incorporated herein by reference. In addition, the expression vectors pKK223-3 and pKK223-2 can be used to express heterologous genes in *E. coli*, either in transcriptional or translational fusion, behind the *tac or trc* promoter. For the expression of operons encoding multiple ORFs, the simplest procedure is to insert the operon into a vector such as pKK223-3 in transcriptional fusion, allowing the cognate ribosome binding site of the heterologous genes to be used. Techniques for overexpression in gram-positive species such as *Bacillus* are also known in the art and can be used in the context of this invention (Quax *et al.*, in: *Industrial Microorganisms: Basic and Applied Molecular Genetics, Eds.* Baltz *et al.*, American Society for Microbiology, Washington (1993)).

Other expression systems that may be used with the epothilone biosynthetic genes of the invention include yeast and baculovirus expression systems. See, for example, "The Expression of Recombinant Proteins in Yeasts," Sudbery, P. E., *Curr. Opin. Biotechnol.* 7(5): 517-524 (1996); "Methods for Expressing Recombinant Proteins in Yeast," Mackay, et al., Editor(s): Carey, Paul R., *Protein Eng. Des.* 105-153, Publisher: Academic, San Diego, Calif (1996); "Expression of heterologous gene products in yeast," Pichuantes, et al., Editor(s): Cleland, J. L., Craik, C. S., *Protein Eng.* 129-161, Publisher: Wiley-Liss, New York, N. Y (1996); WO 98/27203; Kealey *et al., Proc. Natl. Acad. Sci. USA* 95: 505-509 (1998); "Insect Cell Culture: Recent Advances, Bioengineering Challenges And Implications In Protein Production," Palomares, et al., Editor(s): Galindo, Enrique; Ramirez, Octavio T., *Adv. Bioprocess Eng.* Vol. II, Invited Pap. Int. Symp., 2nd (1998) 25-52, Publisher: Kluwer, Dordrecht, Neth; "Baculovirus Expression Vectors," Jarvis, Donald L., Editor(s): Miller, Lois K., *Baculoviruses* 389-431, Publisher: Plenum, New York, N. Y. (1997); "Production Of Heterologous Proteins Using The Baculovirus/Insect Expression System," Grittiths, et al., *Methods Mol. Biol.* (Totowa, N. J.) 75 (Basic Cell Culture Protocols (2nd Edition)) 427-440 (1997); and "Insect Cell Expression Technology," Luckow, Verne A., *Protein Eng.* 183-218,

Publisher: Wiley-Liss, New York, N. Y. (1996); all of which are incorporated herein by reference.

Another consideration for expression of PKS genes in heterologous hosts is the requirement of enzymes for posttranslational modification of PKS enzymes by phosphopantetheinylation before they can synthesize polyketides. However, the enzymes responsible for this modification of type I PKS enzymes, phosphopantetheinyl (P-pant) transferases are not normally present in many hosts such as *E. coli.* This problem can be solved by coexpression of a P-pant transferase with the PKS genes in the heterologous host, as described by Kealey *et al., Proc. Natl. Acad. Sci. USA* 95: 505-509 (1998), incorporated herein by reference.

Therefore, for the purposes of polyketide production, the significant criteria in the choice of host organism are its ease of manipulation, rapidity of growth (*i.e.* fermentation), possession or the proper molecular machinery for processes such as posttranslational modification, and its lack of susceptibility to the polyketide being overproduced. Most preferred host organisms are actinomycetes such as strains of *Streptomyces.* Other preferred host organisms are pseudomonads and *E. coli.* The above-described methods of polyketide production have significant advantages over the technology currently used in the preparation of the compounds. These advantages include the cheaper cost of production, the ability to produce greater quantities of the compounds, and the ability to produce compounds of a preferred biological enantiomer, as opposed to racemic mixtures inevitably generated by organic synthesis. Compounds produced by heterologous hosts can be used in medical (*e.g.* cancer treatment in the case of epothilones) as well as agricultural applications.

EXPERIMENTAL

The invention will be further described by reference to the following detailed examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Standard recombinant DNA and molecular cloning techniques used here are well known in the art and are described by Ausubel (ed.), *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (1994); T. Maniatis, E. F. Fritsch and J. Sambrook, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor laboratory, Cold Spring Harbor, NY (1989); and by T.J. Silhavy, M.L. Berman, and L.W. Enquist, *Experiments with Gene Fusions*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1984).

Example 1: Cultivation of an Epothilone-Producing Strain of *Sorangium cellulosum*

Sorangium cellulosum strain 90 (DSM 6773, Deutsche Sammlung von Mikroorganismen und Zellkulturen, Braunschweig) is streaked out and grown (30°C) on an agar plate of SolE medium (0.35% glucose, 0.05% tryptone, 0.15% $MgSO_4$ x $7H_2O$, 0.05% ammonium sulfate, 0.1% $CaCl_2$, 0.006% K_2HPO_4, 0.01% sodium dithionite, 0.0008% Fe-EDTA, 1.2% HEPES, 3.5% [vol/vol] supernatant of sterilized stationary *S. cellulosum* culture) pH ad. 7.4. Cells from about 1 square cm are picked and inoculated into 5 mls of G51t liquid medium (0.2% glucose, 0.5% starch, 0.2% tryptone, 0.1% probion S, 0.05% $CaCl_2x2H_20$, 0.05% $MgSO_4x7H_20$, 1.2% HEPES, pH ad. 7.4) and incubated at 30°C with shaking at 225 rpm. After 4 days, the culture is transferred into 50 mls of G51t and incubated as above for 5 days. This culture is used to inoculate 500 mls of G51t and incubated as above for 6 days. The culture is centrifuged for 10 minutes at 4000 rpm and the cell pellet is resuspended in 50 mls of G51t.

Example 2: Generation of a Bacterial Artificial Chromosome (Bac) Library

To generate a Bac library, *S. cellulosum* cells cultivated as described in Example 1 above are embedded into agarose blocks, lysed, and the liberated genomic DNA is partially digested by the restriction enzyme *Hin*dIII. The digested DNA is separated on an agarose gel by pulsed-field electrophoresis. Large (approximately 90-150 kb) DNA fragments are

isolated from the agarose gel and ligated into the vector pBelobacII. pBelobacII contains a gene encoding chloramphenicol resistance, a multiple cloning site in the *lacZ* gene providing for blue/white selection on appropriate medium, as well as the genes required for the replication and maintenance of the plasmid at one or two copies per cell. The ligation mixture is used to transform *Escherichia coli* DH10B electrocompetent cells using standard electroporation techniques. Chloramphenicol-resistant recombinant (white, *lacZ* mutant) colonies are transferred to a positively charged nylon membrane filter in 384 3X3 grid format. The clones are lysed and the DNA is cross-linked to the filters. The same clones are also preserved as liquid cultures at -80°C.

Example 3: Screening the Bac Library of *Sorangium cellulosum* 90 for the Presence of Type I Polyketide Synthase-Related Sequences

The Bac library filters are probed by standard Southern hybridization procedures. The DNA probes used encode β-ketoacyl synthase domains from the first and second modules of the rifamycin polyketide synthase (Schupp *et al., FEMS Microbiology Letters* 159: 201-207 (1998)). The probe DNAs are generated by PCR with primers flanking each ketosynthase domain using the plasmid pNE95 as the template (pNE95 equals cosmid 2 described in Schupp et al. (1998)). 25 ng of PCR-amplified DNA is isolated from a 0.5% agarose gel and labeled with ^{32}P-dCTP using a random primer labeling kit (Gibco-BRL, Bethesda MD, USA) according to the manufacturer's instructions. Hybridization is at 65°C for 36 hours and membranes are washed at high stringency (3 times with 0.1x SSC and 0.5% SDS for 20 min at 65°C). The labeled blot is exposed on a phosphorescent screen and the signals are detected on a PhosphoImager 445SI (screen and 445SI from Molecular Dynamics). This results in strong hybridization of certain Bac clones to the probes. These clones are selected and cultured overnight in 5 mls of Luria broth (LB) at 37°C. Bac DNA from the Bac clones of interest is isolated by a typical miniprep procedure. The cells are resuspended in 200 µl lysozyme solution (50mM glucose, 10 mM EDTA, 25 mM Tris-HCl, 5mg/ml lysozyme), lysed in 400 µl lysis solution (0.2 N NaOH and 2% SDS), the proteins are precipitated (3.0 M potassium acetate, adjusted to pH5.2 with acetic acid), and the Bac DNA is precipitated with isopropanol. The DNA is resuspended in 20µl of nuclease-free distilled water, restricted with *Bam*HI (New England Biolabs, Inc.) and separated on a 0.7% agarose gel. The gel is blotted by Southern hybridization as described above and probed

under conditions described above, with a 1.2 kb *Sma*I DNA fragment encoding the ketosynthase domain of the fourth module of the soraphen polyketide synthase as the probe (*see*, U.S. Patent No. 5,716,849). Five different hybridization patterns are observed. One clone representing each of the five patterns is selected and named pEPO15, pEPO20, pEPO30, pEPO31, and pEPO33, respectively.

Example 4: Subcloning of *Bam*HI Fragments from pEPO15, pEPO20, pEPO30, pEPO31, and pEPO33

The DNA of the five selected Bac clones is digested with *Bam*HI and random fragments are subcloned into pBluescript II SK+ (Stratagene) at the *Bam*HI site. Subclones carrying inserts between 2 and 10 kb in size are selected for sequencing of the flanking ends of the inserts and also probed with the 1.2 *Sma*I probe as described above. Subclones that show a high degree of sequence homology to known polyketide synthases and/or strong hybridization to the soraphen ketosynthase domain are used for gene disruption experiments.

Example 5: Preparation of Streptomycin-Resistant Spontaneous Mutants of *Sorangium cellulosum* strain So ce90

0.1 ml of a three day old culture of *Sorangium cellulosum* strain So ce90, which is raised in liquid medium G52-H (0.2% yeast extract, 0.2% soyameal defatted, 0.8% potato starch, 0.2% glucose, 0.1% $MgSO_4 \times 7H_2O$, 0.1% $CaCl_2 \times 2H_2O$, 0.008% Fe-EDTA, pH ad 7.4 with KOH), is plated out on agar plates with SolE medium supplemented with 100 µg/ml streptomycin. The plates are incubated at 30°C for 2 weeks. The colonies growing on this medium are streptomycin-resistant mutants, which are streaked out and cultivated once more on the same agar medium with streptomycin for purification. One of these streptomycin-resistant mutants is selected and is called BCE28/2.

Example 6: Gene Disruptions in *Sorangium cellulosum* BCE28/2 Using the Subcloned *Bam*HI Fragments

The *Bam*HI inserts of the subclones generated from the five selected Bac clones as described above are isolated and ligated into the unique *Bam*HI site of plasmid pCIB132 (*see*, U.S. Patent No. 5,716,849). The pCIB132 derivatives carrying the inserts are transformed into Escherichia coli ED8767 containing the helper plasmid pUZ8 (Hedges and Matthew, *Plasmid* 2: 269-278 (1979). The transformants are used as donors in conjugation experiments with *Sorangium cellulosum* BCE28/2 as recipient. For the conjugation, 5-10 x 10^9 cells of *Sorangium cellulosum* BCE28/2 from an early stationary phase culture (reaching about 5 x 10^8 cells/ml) grown at 30°C in liquid medium G51b (G51b equals medium G51t with tryptone replaced by peptone) are mixed in a 1:1 cellular ratio with a late-log phase culture (in LB liquid medium) of *E. coli* ED8767 containing pCIB132 derivatives carrying the subcloned *Bam*HI fragments and the helper plasmid pUZ8. The mixed cells are then centrifuged at 4000 rpm for 10 minutes and resuspended in 0.5 ml G51b medium. This cell suspension is then plated as a drop in the center of a plate with So1E agar containg 50 mg/l kanamycin. The cells obtained after incubation for 24 hours at 30°C are harvested and resuspended in 0.8 ml of G51b medium, and 0.1 to 0.3 ml of this suspension is plated out on a selective So1E solid medium containing phleomycin (30 mg/l), streptomycin (300 mg/l), and kanamycin (50 mg/l). The counterselection of the donor *Escherichia coli* strain takes place with the aid of streptomycin. The colonies that grow on this selective medium after an incubation time of 8-12 days at a temperature of 30°C are isolated with a plastic loop and streaked out and cultivated on the same agar medium for a second round of selection and purification. The colony-derived cultures that grow on this selective agar medium after 7 days at a temperature of 30°C are transconjugants of *Sorangium cellulosum* BCE28/2 that have acquired phleomycin resistance by conjugative transfer of the pCIB132 derivatives carrying the subcloned *Bam*HI fragments.

Integration of the pCIB132-derived plasmids into the chromosome of *Sorangium cellulosum* BCE28/2 by homologous recombination is verified by Southern hybridization. For this experiment, complete DNA from 5-10 tranconjugants per transferred *Bam*HI fragment is isolated (from 10 ml cultures grown in medium G52-H for three days) applying the method described by Pospiech and Neumann, *Trends Genet.* 11: 217 (1995). For the Southern blot, the DNA isolated as described above is cleaved either with the restriction

enzymes *BglII*, *ClaI*, or *NotI*, and the respective *Bam*HI inserts or pCIB132 are used as 32P labelled probes.

Example 7: Analysis of the Effect of the Integrated *Bam*HI Fragments on Epothilone Production by *Sorangium cellulosum* After Gene Disruption

Transconjugant cells grown on about 1 square cm surface of the selective So1E plates of the second round of selection (see Example 6) are transferred by a sterile plastic loop into 10 ml of medium G52-H in an 50 ml Erlenmeyer flask. After incubation at 30°C and 180 rpm for 3 days, the culture is transfered into 50 ml of medium G52-H in an 200 ml Erlenmeyer flask. After incubation at 30°C and 180 rpm for 4-5 days, 10 ml of this culture is transfered into 50 ml of medium 23B3 (0.2 % glucose, 2 % potato starch, 1.6 % soya meal defatted, 0.0008 % Fe-EDTA Sodium salt, 0.5 % HEPES (4-(2-hydroxyethyl)-piperazine-1-ethane-sulfonic-acid), 2 % vol/vol polysterole resin XAD16 (Rohm & Haas), pH adjusted to 7.8 with NaOH) in an 200 ml Erlenmeyer flask.

Quantitative determination of the epothilone produced takes place after incubation of the cultures at 30°C and 180 rpm for 7 days. The complete culture broth is filtered by suction through a 150 µm nylon filter. The resin remaining on the filter is then resuspended in 10 ml isopropanol and extracted by shaking the suspension at 180 rpm for 1 hour. 1 ml is removed from this suspension and centrifuged at 12,000 rpm in an Eppendorff Microfuge. The amount of epothilones A and B therein is determined by means of an HPLC and detection at 250 nm with a UV_DAD detector (HPLC with Waters -Symetry C18 column and a gradient of 0.02 % phosphoric acid 60%-0% and acetonitril 40%-100%).

Transconjugants with three different integrated *Bam*HI fragments subcloned from pEPO15, namely transconjugants with the *Bam*HI fragment of plasmid pEPO15-21, transconjugants with the *Bam*HI fragment of plasmid pEPO15-4-5, and transconjugants with the *Bam*HI fragment of plasmid pEPO15-4-1, are tested in the manner described above. HPLC analysis reveals that all transconjugants no longer produce epothilone A or B. By contrast, epothilone A and B are detectable in a concentration of 2-4 mg/l in transconjugants with *Bam*HI fragments integrated that are derived from pEPO20, pEPO30, pEPO31, pEPO33, and in the parental strain BCE28/2.

Example 8: Nucleotide Sequence Determination of the Cloned Fragments and Construction of Contigs

A. *Bam*HI Insert of Plasmid pEPO15-21

Plasmid DNA is isolated from the strain *Escherichia coli* DH10B [pEPO15-21], and the nucleotide sequence of the 2.3-kb *Bam*HI insert in pEPO15-21 is determined. Automated DNA sequencing is done on the double-stranded DNA template by the dideoxynucleotide chain termination method, using Applied Biosystems model 377 sequencers. The primers used are the universal reverse primer (5' GGA AAC AGC TAT GAC CAT G 3' (SEQ ID NO:24)) and the universal forward primer (5' GTA AAA CGA CGG CCA GT 3' (SEQ ID NO:25)). In subsequent rounds of sequencing reactions, custom-synthesized oligonucleotides, designed for the 3' ends of the previously determined sequences, are used to extend and join contigs. Both strands are entirely sequenced, and every nucleotide is sequenced at least two times. The nucleotide sequence is compiled using the program Sequencher vers. 3.0 (Gene Codes Corporation), and analyzed using the University of Wisconsin Genetics Computer Group programs. The nucleotide sequence of the 2213-bp insert corresponds to nucleotides 20779-22991 of SEQ ID NO:1.

B. *Bam*HI Insert of Plasmid pEPO15-4-1

Plasmid DNA is isolated from the strain *Escherichia coli* DH10B [pEPO15-4-1], and the nucleotide sequence of the 3.9-kb *Bam*HI insert in pEPO15-4-1 is determined as described in (A) above. The nucleotide sequence of the 3909-bp insert corresponds to nucleotides 16876-20784 of SEQ ID NO:1.

C. *Bam*HI Insert of Plasmid pEPO15-4-5

Plasmid DNA is isolated from the strain *Escherichia coli* DH10B [pEPO15-4-5], and the nucleotide sequence of the 2.3-kb *Bam*HI insert in pEPO15-4-5 is determined as described in (A) above. The nucleotide sequence of the 2233-bp insert corresponds to nucleotides 42528-44760 of SEQ ID NO:1.

Example 9: Subcloning and Ordering of DNA Fragments from pEPO15 Containing Epothilone Biosynthesis Genes

pEPO15 is digested to completion with the restriction enzyme *Hin*dIII and the resulting fragments are subcloned into pBluescript II SK- or pNEB193 (New England Biolabs) that has been cut with *Hin*dIII and dephosphorylated with calf intestinal alkaline phosphatase. Six different clones are generated and named pEPO15-NH1, pEPO15-NH2, pEPO15-NH6, pEPO15-NH24 (all based on pNEB193), and pEPO15-H2.7 and pEPO15-H3.0 (both based on pBluescript II SK-).

The *Bam*HI insert of pEPO15-21 is isolated and DIG-labeled (Non-radioactive DNA labeling and detection system, Boehringer Mannheim), and used as a probe in DNA hybridization experiments at high stringency against pEPO15-NH1, pEPO15-NH2, pEPO15-NH6, pEPO15-NH24, pEPO15-H2.7 and pEPO15-H3.0. Strong hybridization signal is detected for pEPO15-NH24, indicating that pEPO15-21 is contained within pEPO15-NH24.

The *Bam*HI insert of pEPO15-4-1 is isolated and DIG-labeled as above, and used as a probe in DNA hybridization experiments at high stringency against pEPO15-NH1, pEPO15-NH2, pEPO15-NH6, pEPO15-NH24, pEPO15-H2.7 and pEPO15-H3.0. Strong hybridization signals are detected for pEPO15-NH24 and pEPO15-H2.7. Nucleotide sequence data generated from one end each of pEPO15-NH24 and pEPO15-H2.7 are also in complete agreement with the previously determined sequence of the *Bam*HI insert of pEPO15-4-1. These experiments demonstrate that pEPO15-4-1 (which contains one internal *Hin*dIII site) overlaps pEPO15-H2.7 and pEPO15-NH24, and that pEPO15-H2.7 and pEPO15-NH24, in this order, are contiguous.

The *Bam*HI insert of pEPO15-4-5 is isolated and DIG-labeled as above, and used as a probe in DNA hybridization experiments at high stringency against pEPO15-NH1, pEPO15-NH2, pEPO15-NH6, pEPO15-NH24, pEPO15-H2.7 and pEPO15-H3.0. Strong hybridization signal is detected for pEPO15-NH2, indicating that pEPO15-21 is contained within pEPO15-NH2.

Nucleotide sequence data is generated from both ends of pEPO15-NH2 and from the end of pEPO15-NH24 that does not overlap with pEPO15-4-1. PCR primers NH24 end "B": GTGACTGGCGCCTGGAATCTGCATGAGC (SEQ ID NO:26), NH2 end "A": AGCGGGAGCTTGCTAGACATTCTGTTTC (SEQ ID NO:27), and NH2 end "B": GACGCGCCTCGGGCAGCGCCCCAA (SEQ ID NO:28), pointing towards the *Hin*dIII sites,

are designed based on these sequences and used in amplification reactions with pEPO15 and, in separate experiments, with *Sorangium cellulosum* So ce90 genomic DNA as the templates. Specific amplification is found with primer pair NH24 end "B" and NH2 end "A" with both templates. The amplimers are cloned into pBluescript II SK- and completely sequenced. The sequences of the amplimers are identical, and also agree completely with the end sequences of pEPO15-NH24 and pEPO15-NH2, fused at the *Hin*dIII site, establishing that the *Hin*dIII fragments of pEPO15-NH2 and pEPO15-NH24 are, in this order, contiguous.

The *Hin*dIII insert of pEPO15-H2.7 is isolated and DIG-labeled as above, and used as a probe in a DNA hybridization experiment at high stringency against pEPO15 digested by *Not*I. A *Not*I fragment of about 9 kb in size shows a strong a hybridization, and is further subcloned into pBluescript II SK- that has been digested with *Not*I and dephosphorylated with calf intestinal alkaline phosphatase, to yield pEPO15-N9-16. The *Not*I insert of pEPO15-N9-16 is isolated and DIG-labeled as above, and used as a probe in DNA hybridization experiments at high stringency against pEPO15-NH1, pEPO15-NH2, pEPO15-NH6, pEPO15-NH24, pEPO15-H2.7 and pEPO15-H3.0. Strong hybridization signals are detected for pEPO15-NH6, and also for the expected clones pEPO15-H2.7 and pEPO15-NH24. Nucleotide sequence data is generated from both ends of pEPO15-NH6 and from the end of pEPO15-H2.7 that does not overlap with pEPO15-4-1. PCR primers are designed pointing towards the *Hin*dIII sites and used in amplification reactions with pEPO15 and, in separate experiments, with *Sorangium cellulosum* So ce90 genomic DNA as the templates. Specific amplification is found with primer pair pEPO15-NH6 end "B": CACCGAAGCGTCGATCTGGTCCATC (SEQ ID NO:29) and pEPO15-H2.7 end "A": CGGTCAGATCGACGACGGGCTTTCC (SEQ ID NO:30) with both templates. The amplimers are cloned into pBluescript II SK- and completely sequenced. The sequences of the amplimers are identical, and also agree completely with the end sequences of pEPO15-NH6 and pEPO15-H2.7, fused at the *Hin*dIII site, establishing that the *Hin*dIII fragments of pEPO15-NH6 and pEPO15-H2.7 are, in this order, contiguous.

All of these experiments, taken together, establish a contig of *Hin*dIII fragments covering a region of about 55 kb and consisting of the *Hin*dIII inserts of pEPO15-NH6, pEPO15-H2.7, pEPO15-NH24, and pEPO15-NH2, in this order. The inserts of the remaining two *Hin*dIII subclones, namely pEPO15-NH1 and pEPO15-H3.0, are not found to be parts of this contig.

Example 10: Further Extension of the Subclone Contig Covering the Epothilone Biosynthesis Genes

An approximately 2.2 kb *Bam*HI – *Hin*dIII fragment derived from the downstream end of the insert of pEPO15-NH2 and thus representing the downstream end of the subclone contig described in Example 9 is isolated, DIG-labeled, and used in Southern hybridization experiments against pEPO15 and pEPO15-NH2 DNAs digested with several enzymes. The strongly hybridizing bands are always found to be the same in size between the two target DNAs indicating that the *Sorangium cellulosum* So ce90 genomic DNA fragment cloned into pEPO15 ends with the *Hin*dIII site at the downstream end of pEPO15-NH2.

A cosmid DNA library of *Sorangium cellulosum* So ce90 is generated, using established procedures, in pScosTriplex-II (Ji, *et al., Genomics* 31: 185-192 (1996)). Briefly, high-molecular weight genomic DNA of *Sorangium cellulosum* So ce90 is partially digested with the restriction enzyme *Sau*3AI to provide fragments with average sizes of about 40 kb, and ligated to *Bam*HI and *Xba*I digested pScosTriplex-II. The ligation mix is packaged with Gigapack III XL (Stratagene) and used to transfect *E. coli* XL1 Blue MR cells.

The cosmid library is screened with the approximately 2.2 kb *Bam*HI – *Hin*dIII fragment, derived from the downstream end of the insert of pEPO15-NH2, used as a probe in colony hybridization. A strongly hybridizing clone, named pEPO4E7 is selected.

pEPO4E7 DNA is isolated, digested with several restriction endonucleases, and probed in Southern hybridization experiments with the 2.2 kb *Bam*HI – *Hin*dIII fragment. A strongly hybridizing *Not*I fragment of approximately 9 kb in size is selected and subcloned into pBluescript II SK- to yield pEPO4E7-N9-8. Further Southern hybridization experiments reveal that the approximately 9 kb *Not*I insert of pEPO4E7-N9-8 overlaps pEPO15-NH2 over 6 kb in a *Not*I – *Hin*dIII fragment, while the remaining approximately 3 kb *Hin*dIII – *Not*I fragment would extend the subclone contig described in Example 9. End sequencing reveals, however, that the downstream end of the insert of pEPO4E7-N9-8 contains the *Bam*HI – *Not*I polylinker of pScosTriplex-II, thereby indicating that the genomic DNA insert of pEPO4E7 ends at a *Sau*3AI site within the extending *Hin*dIII – *Not*I fragment and that the *Not*I site is derived from pScosTriplex-II.

An approximately 1.6 kb *Pst*I – *Sal*I fragment derived from the approximately 3 kb extending *Hin*dIII – *Not*I subfragment of pEPO4E7-N9-8, containing only *Sorangium*

cellulosum So ce90–derived sequences free of vector, is used as a probe against the bacterial artificial chromosome library described in Example 2. Besides the previously-isolated EPO15, a Bac clone, named EPO32, is found to strongly hybridize to the probe. pEPO32 is isolated, digested with several restriction endonucleases, and hybridized with the approximately 1.6 kb *Pst*I – *Sal*I probe. A *Hin*dIII – *Eco*RV fragment of about 13 kb in size is found to strongly hybridize to the probe, and is subcloned into pBluescript II SK- digested with *Hin*dIII and *Hin*cII to yield pEPO32-HEV15.

Oligonucleotide primers are designed based on the downstream end sequence of pEPO15-NH2 and on the upstream (*Hin*dIII) end sequence derived from pEPO32-HEV15, and used in sequencing reactions with pEPO4E7-N9-8 as the template. The sequences reveal the existence of a small *Hin*dIII fragment (EPO4E7-H0.02) of 24 bp, undetectable in standard restriction analysis, separating the *Hin*dIII site at the downstream end of pEPO15-NH2 from the *Hin*dIII site at the upstream end of pEPO32-HEV15.

Thus, the subclone contig described in Example 9 is extended to include the *Hin*dIII fragment EPO4E7-H0.02 and the insert of pEPO32-HEV15, and constitutes the inserts of: pEPO15-NH6, pEPO15-H2.7, pEPO15-NH24, pEPO15-NH2, EPO4E7-H0.02 and pEPO32-HEV15, in this order.

Example 11: Nucleotide Sequence Determination of the Subclone Contig Covering the Epothilone Biosynthesis Genes

The nucleotide sequence of the subclone contig described in Example 10 is determined as follows.

pEPO15-H2.7. Plasmid DNA is isolated from the strain *Escherichia coli* DH10B [pEPO15-H2.7], and the nucleotide sequence of the 2.7-kb *Bam*HI insert in pEPO15-H2.7 is determined. Automated DNA sequencing is done on the double-stranded DNA template by the dideoxynucleotide chain termination method, using Applied Biosystems model 377 sequencers. The primers used are the universal reverse primer (5' GGA AAC AGC TAT GAC CAT G 3' (SEQ ID NO:24)) and the universal forward primer (5' GTA AAA CGA CGG CCA GT 3' (SEQ ID NO:25)). In subsequent rounds of sequencing reactions, custom-synthesized oligonucleotides, designed for the 3' ends of the previously determined sequences, are used to extend and join contigs.

pEPO15-NH6, pEPO15-NH24 and pEPO15-NH2. The *Hin*dIII inserts of these plasmids are isolated, and subjected to random fragmentation using a Hydroshear apparatus (Genomic Instrumentation Services, Inc.) to yield an average fragment size of 1-2 kb. The fragments are end-repaired using T4 DNA Polymerase and Klenow DNA Polymerase enzymes in the presence of desoxynucleotide triphosphates, and phosphorylated with T4 DNA Kinase in the presence of ribo-ATP. Fragments in the size range of 1.5-2.2 kb are isolated from agarose gels, and ligated into pBluescript II SK- that has been cut with *Eco*RV and dephosphorylated. Random subclones are sequenced using the universal reverse and the universal forward primers.

pEPO32-HEV15. pEPO32-HEV15 is digested with *Hin*dIII and *Ssp*I, the approximately 13.3 kb fragment containing the ~13 kb *Hin*dIII – *Eco*RV insert from *So. cellulosum* So ce90 and a 0.3 kb *Hin*cII – *Ssp*I fragment from pBluescript II SK- is isolated, and partially digested with *Hae*III to yield fragments with an average size of 1-2 kb. Fragments in the size range of 1.5-2.2 kb are isolated from agarose gels, and ligated into pBluescript II SK- that has been cut with *Eco*RV and dephosphorylated. Random subclones are sequenced using the universal reverse and the universal forward primers.

The chromatograms are analyzed and assembled into contigs with the Phred, Phrap and Consed programs (Ewing, *et al., Genome Res.* 8(3): 175-185 (1998); Ewing, *et al., Genome Res.* 8(3): 186-194 (1998); Gordon, *et al., Genome Res.* 8(3): 195-202 (1998)). Contig gaps are filled, sequence discrepancies are resolved, and low-quality regions are resequenced using custom-designed oligonucleotide primers for sequencing on either the original subclones or selected clones from the random subclone libraries. Both strands are completely sequenced, and every basepair is covered with at least a minimum aggregated Phred score of 40 (confidence level of 99.99%).

The nucleotide sequence of the 68750 bp contig is shown as SEQ ID NO:1.

Example 12: Nucleotide Sequence Analysis of the Epothilone Biosynthesis Genes

SEQ ID NO:1 is found to contain 22 ORFs as detailed below in Table 1:

Table 1

ORF	Start codon	Stop codon	Homology of deduced protein	Proposed function of deduced protein
*orf*1	outside of sequenced range	1826		
*orf*2 *	3171	1900	Hypothetical protein SP: Q11037; DD-peptidase SP:P15555	
*orf*3	3415	5556	*Na/H antiporter PID: D1017724*	*Transport*
*orf*4 *	5992	5612		
*orf*5	6226	6675		
*epo*A	7610	11875	Type I polyketide synthase	Epothilone synthase: Thiazole ring formation
*epo*P	11872	16104	Non-ribosomal peptide synthetase	Epothilone synthase: Thiazole ring formation
*epo*B	16251	21749	Type I polyketide synthase	Epothilone synthase: Polyketide backbone formation
*epo*C	21746	43519	Type I polyketide synthase	Epothilone synthase: Polyketide backbone formation
*epo*D	43524	54920	Type I polyketide synthase	Epothilone synthase: Polyketide backbone formation
*epo*E	54935	62254	Type I polyketide synthase	Epothilone synthase: Polyketide backbone formation
*epo*F	62369	63628	Cytochrome P450	Epothilone macrolactone oxidase
*orf*6	63779	64333		
*orf*7 *	64290	63853		
*orf*8	64363	64920		
*orf*9 *	64727	64287		
*orf*10	65063	65767		
*orf*11 *	65874	65008		
*orf*12 *	66338	65871		
*orf*13	66667	67137		
*orf*14	67334	68251	Hypothetical protein GI:3293544; Cation efflux system protein GI:2623026	Transport
*orf*15	68346	outside of sequenced range		

* On the reverse complementer strand. Numbering according to SEQ ID NO:1.

*epo*A (nucleotides 7610-11875 of SEQ ID NO:1) codes for EPOS A (SEQ ID NO:2), a type I polyketide synthase consisting of a single module, and harboring the following domains: β-ketoacyl-synthase (KS) (nucleotides 7643-8920 of SEQ ID NO:1, amino acids 11-

437 of SEQ ID NO:2); acyltransferase (AT) (nucleotides 9236-10201 of SEQ ID NO:1, amino acids 543-864 of SEQ ID NO:2); enoyl reductase (ER) (nucleotides 10529-11428 of SEQ ID NO:1, amino acids 974-1273 of SEQ ID NO:2); and acyl carrier protein homologous domain (ACP) (nucleotides 11549-11764 of SEQ ID NO:1, amino acids 1314-1385 of SEQ ID NO:2). Sequence comparisons and motif analysis (Haydock, et al. *FEBS Lett.* 374: 246-248 (1995); Tang, et al., *Gene* 216: 255-265 (1998)) reveal that the AT encoded by EPOS A is specific for malonyl-CoA. EPOS A should be involved in the initiation of epothilone biosynthesis by loading the acetate unit to the multienzyme complex that will eventually form part of the 2-methylthiazole ring (C26 and C20).

*epo*P (nucleotides 11872-16104 of SEQ ID NO:1) codes for EPOS P (SEQ ID NO:3), a non-ribosomal peptide synthetase containing one module. EPOS P harbors the following domains:

- peptide bond formation domain, as delineated by motif K (amino acids 72-81 [FPLTDIQESY] of SEQ ID NO:3, corresponding to nucleotide positions 12085-12114 of SEQ ID NO:1); motif L (amino acids 118-125 [VVARHDML] of SEQ ID NO:3, corresponding to nucleotide positions 12223-12246 of SEQ ID NO:1); motif M (amino acids 199-212 [SIDLINVDLGSLSI] of SEQ ID NO:3, corresponding to nucleotide positions 12466-12507 of SEQ ID NO:1); and motif O (amino acids 353-363 [GDFTSMVLLDI] of SEQ ID NO:3, corresponding to nucleotide positions 12928-12960 of SEQ ID NO:1);
- aminoacyl adenylate formation domain, as delineated by motif A (amino acids 549-565 [LTYEELSRRSRRLGARL] of SEQ ID NO:3, corresponding to nucleotide positions 13516-13566 of SEQ ID NO:1); motif B (amino acids 588-603 [VAVLAVLESGAAYVPI] of SEQ ID NO:3, corresponding to nucleotide positions 13633-13680 of SEQ ID NO:1); motif C (amino acids 669-684 [AYVIYTSGSTGLPKGV] of SEQ ID NO:3, corresponding to nucleotide positions 13876-13923 of SEQ ID NO:1); motif D (amino acids 815-821 [SLGGATE] of SEQ ID NO:3, corresponding to nucleotide positions 14313-14334 of SEQ ID NO:1); motif E (amino acids 868-892 [GQLYIGGVGLALGYWRDEEKTRKSF] of SEQ ID NO:3, corresponding to nucleotide positions 14473-14547 of SEQ ID NO:1); motif F (amino acids 903-912 [YKTGDLGRYL] of SEQ ID NO:3, corresponding to nucleotide positions 14578-14607 of SEQ ID NO:1); motif G (amino acids 918-940 [EFMGREDNQIKLRGYRVELGEIE] of SEQ ID NO:3, corresponding to nucleotide positions 14623-14692 of SEQ ID NO:1); motif H (amino acids 1268-1274 [LPEYMVP] of SEQ ID NO:3, corresponding to nucleotide positions 15673-15693 of SEQ ID NO:1); and

motif I (amino acids 1285-1297 [LTSNGKVDRKALR] of SEQ ID NO:3, corresponding to nucleotide positions 15724-15762 of SEQ ID NO:1);

- an unknown domain, inserted between motifs G and H of the aminoacyl adenylate formation domain (amino acids 973-1256 of SEQ ID NO:3, corresponding to nucleotide positions 14788-15639 of SEQ ID NO:1); and
- a peptidyl carrier protein homologous domain (PCP), delineated by motif J (amino acids 1344-1351 [GATSIHIV] of SEQ ID NO:3, corresponding to nucleotide positions 15901-15924 of SEQ ID NO:1).

It is proposed that EPOS P is involved in the activation of a cysteine by adenylation, binding the activated cysteine as an aminoacyl-S-PCP, forming a peptide bond between the enzyme-bound cysteine and the acetyl-S-ACP supplied by EPOS A, and the formation of the initial thiazoline ring by intramolecular heterocyclization. The unknown domain of EPOS P displays very weak homologies to NAD(P)H oxidases and reductases from Bacillus species. Thus, this unknown domain and/or the ER domain of EPOS A may be involved in the oxidation of the initial 2-methylthiazoline ring to a 2-methylthiazole.

*epo*B (nucleotides 16251-21749 of SEQ ID NO:1) codes for EPOS B (SEQ ID NO:4), a type I polyketide synthase consisting of a single module, and harboring the following domains: KS (nucleotides 16269-17546 of SEQ ID NO:1, amino acids 7-432 of SEQ ID NO:4); AT (nucleotides 17865-18827 of SEQ ID NO:1, amino acids 539-859 of SEQ ID NO:4); dehydratase (DH) (nucleotides 18855-19361 of SEQ ID NO:1, amino acids 869-1037 of SEQ ID NO:4); β-ketoreductase (KR) (nucleotides 20565-21302 of SEQ ID NO:1, amino acids 1439-1684 of SEQ ID NO:4); and ACP (nucleotides 21414-21626 of SEQ ID NO:1, amino acids 1722-1792 of SEQ ID NO:4). Sequence comparisons and motif analysis reveal that the AT encoded by EPOS B is specific for methylmalonyl-CoA. EPOS A should be involved in the first polyketide chain extension by catalysing the Claisen-like condensation of the 2-methyl-4-thiazolecarboxyl-S-PCP starter group with the methylmalonyl-S-ACP, and the concomitant reduction of the b-keto group of C17 to an enoyl.

*epo*C (nucleotides 21746-43519 of SEQ ID NO:1) codes for EPOS C (SEQ ID NO:5), a type I polyketide synthase consisting of 4 modules. The first module harbors a KS (nucleotides 21860-23116 of SEQ ID NO:1, amino acids 39-457 of SEQ ID NO:5); a malonyl CoA-specific AT (nucleotides 23431-24397 of SEQ ID NO:1, amino acids 563-884 of SEQ ID NO:5); a KR (nucleotides 25184-25942 of SEQ ID NO:1, amino acids 1147-1399 of SEQ ID NO:5); and an ACP (nucleotides 26045-26263 of SEQ ID NO:1, amino acids 1434-1506 of

SEQ ID NO:5). This module incorporates an acetate extender unit (C14-C13) and reduces the β-keto group at C15 to the hydroxyl group that takes part in the final lactonization of the epothilone macrolactone ring. The second module of EPOS C harbors a KS (nucleotides 26318-27595 of SEQ ID NO:1, amino acids 1524-1950 of SEQ ID NO:5); a malonyl CoA-specific AT (nucleotides 27911-28876 of SEQ ID NO:1, amino acids 2056-2377 of SEQ ID NO:5); a KR (nucleotides 29678-30429 of SEQ ID NO:1, amino acids 2645-2895 of SEQ ID NO:5); and an ACP (nucleotides 30539-30759 of SEQ ID NO:1, amino acids 2932-3005 of SEQ ID NO:5). This module incorporates an acetate extender unit (C12-C11) and reduces the β-keto group at C13 to a hydroxyl group. Thus, the nascent polyketide chain of epothilone corresponds to epothilone A, and the incorporation of the methyl side chain at C12 in epothilone B would require a post-PKS C-methyltransferase activity. The formation of the epoxi ring at C13-C12 would also require a post-PKS oxidation step. The third module of EPOS C harbors a KS (nucleotides 30815-32092 of SEQ ID NO:1, amino acids 3024-3449 of SEQ ID NO:5); a malonyl CoA-specific AT (nucleotides 32408-33373 of SEQ ID NO:1, amino acids 3555-3876 of SEQ ID NO:5); a DH (nucleotides 33401-33889 of SEQ ID NO:1, amino acids 3886-4048 of SEQ ID NO:5); an ER (nucleotides 35042-35902 of SEQ ID NO:1, amino acids 4433-4719 of SEQ ID NO:5); a KR (nucleotides 35930-36667 of SEQ ID NO:1, amino acids 4729-4974 of SEQ ID NO:5); and an ACP (nucleotides 36773-36991 of SEQ ID NO:1, amino acids 5010-5082 of SEQ ID NO:5). This module incorporates an acetate extender unit (C10-C9) and fully reduces the β-keto group at C11. The fourth module of EPOS C harbors a KS (nucleotides 37052-38320 of SEQ ID NO:1, amino acids 5103-5525 of SEQ ID NO:5); a methylmalonyl CoA-specific AT (nucleotides 38636-39598 of SEQ ID NO:1, amino acids 5631-5951 of SEQ ID NO:5); a DH (nucleotides 39635-40141 of SEQ ID NO:1, amino acids 5964-6132 of SEQ ID NO:5); an ER (nucleotides 41369-42256 of SEQ ID NO:1, amino acids 6542-6837 of SEQ ID NO:5); a KR (nucleotides 42314-43048 of SEQ ID NO:1, amino acids 6857-7101 of SEQ ID NO:5); and an ACP (nucleotides 43163-43378 of SEQ ID NO:1, amino acids 7140-7211 of SEQ ID NO:5). This module incorporates a propionate extender unit (C24 and C8-C7) and fully reduces the β-keto group at C9.

*epo*D (nucleotides 43524-54920 of SEQ ID NO:1) codes for EPOS D (SEQ ID NO:6), a type I polyketide synthase consisting of 2 modules. The first module harbors a KS (nucleotides 43626-44885 of SEQ ID NO:1, amino acids 35-454 of SEQ ID NO:6); a methylmalonyl CoA-specific AT (nucleotides 45204-46166 of SEQ ID NO:1, amino acids 561-881 of SEQ ID NO:6); a KR (nucleotides 46950-47702 of SEQ ID NO:1, amino acids

1143-1393 of SEQ ID NO:6); and an ACP (nucleotides 47811-48032 of SEQ ID NO:1, amino acids 1430-1503 of SEQ ID NO:6). This module incorporates a propionate extender unit (C23 and C6-C5) and reduces the β-keto group at C7 to a hydoxyl group. The second module harbors a KS (nucleotides 48087-49361 of SEQ ID NO:1, amino acids 1522-1946 of SEQ ID NO: 6); a methylmalonyl CoA-specific AT (nucleotides 49680-50642 of SEQ ID NO:1, amino acids 2053-2373 of SEQ ID NO:6); a DH (nucleotides 50670-51176 of SEQ ID NO:1, amino acids 2383-2551 of SEQ ID NO:6); a methyltransferase (MT, nucleotides 51534-52657 of SEQ ID NO:1, amino acids 2671-3045 of SEQ ID NO:6); a KR (nucleotides 53697-54431 of SEQ ID NO:1, amino acids 3392-3636 of SEQ ID NO:6); and an ACP (nucleotides 54540-54758 of SEQ ID NO:1, amino acids 3673-3745 of SEQ ID NO:6). This module incorporates a propionate extender unit (C21 or C22 and C4-C3) and reduces the β-keto group at C5 to a hydoxyl group. This reduction is somewhat unexpected, since epothilones contain a keto group at C5. Discrepancies of this kind between the deduced reductive capabilities of PKS modules and the redox state of the corresponding positions in the final polyketide products have been, however, reported in the literature (see, for example, Schwecke, et al., *Proc. Natl. Acad. Sci. USA* 92: 7839-7843 (1995) and Schupp, et al., *FEMS Microbiology Letters* 159: 201-207 (1998)). An important feature of epothilones is the presence of gem-methyl side groups at C4 (C21 and C22). The second module of EPOS D is predicted to incorporate a propionate unit into the growing polyketide chain, providing one methyl side chain at C4. This module also contains a methyltransferase domain integrated into the PKS between the DH and the KR domains, in an arrangement similar to the one seen in the HMWP1 yersiniabactin synthase (Gehring, A.M., DeMoll, E., Fetherston, J.D., Mori, I., Mayhew, G.F., Blattner, F.R., Walsh, C.T., and Perry, R.D.: Iron acquisition in plague: modular logic in enzymatic biogenesis of yersiniabactin by Yersinia pestis. *Chem. Biol.* 5, 573-586, 1998). This MT domain in EPOS D is proposed to be responsible for the incorporation of the second methyl side group (C21 or C22) at C4.

*epo*E (nucleotides 54935-62254 of SEQ ID NO:1) codes for EPOS E (SEQ ID NO:7), a type I polyketide synthase consisting of one module, harboring a KS (nucleotides 55028-56284 of SEQ ID NO:1, amino acids 32-450 of SEQ ID NO:7); a malonyl CoA-specific AT (nucleotides 56600-57565 of SEQ ID NO:1, amino acids 556-877 of SEQ ID NO:7); a DH (nucleotides 57593-58087 of SEQ ID NO:1, amino acids 887-1051 of SEQ ID NO:7); a probably nonfunctional ER (nucleotides 59366-60304 of SEQ ID NO:1, amino acids 1478-1790 of SEQ ID NO:7); a KR (nucleotides 60362-61099 of SEQ ID NO:1, amino acids 1810-2055

of SEQ ID NO:7); an ACP (nucleotides 61211-61426 of SEQ ID NO:1, amino acids 2093-2164 of SEQ ID NO:7); and a thioesterase (TE) (nucleotides 61427-62254 of SEQ ID NO:1, amino acids 2165-2439 of SEQ ID NO:7). The ER domain in this module harbors an active site motif with some highly unusual amino acid substitutions that probably render this domain inactive. The module incorporates an acetate extender unit (C2-C1), and reduces the β-keto at C3 to an enoyl group. Epothilones contain a hydroxyl group at C3, so this reduction also appears to be excessive as discussed for the second module of EPOS D. The TE domain of EPOS E takes part in the release and cyclization of the grown polyketide chain via lactonization between the carboxyl group of C1 and the hydroxyl group of C15.

Five ORFs are detected upstream of *epo*A in the sequenced region. The partially sequenced *orf*1 has no homologues in the sequence databanks. The deduced protein product (Orf 2, SEQ ID NO:10) of *orf*2 (nucleotides 3171-1900 on the reverse complement strand of SEQ ID NO:1) shows strong similarities to hypothetical ORFs from *Mycobacterium* and *Streptomyces coelicolor*, and more distant similarities to carboxypeptidases and DD-peptidases of different bacteria. The deduced protein product of *orf*3 (nucleotides 3415-5556 of SEQ ID NO:1), Orf 3 (SEQ ID NO:11), shows homologies to Na/H antiporters of different bacteria. Orf 3 might take part in the export of epothilones from the producer strain. *orf*4 and *orf*5 have no homologues in the sequence databanks.

Eleven ORFs are found downstream of *epo*E in the sequenced region. *epo*F (nucleotides 62369-63628 of SEQ ID NO:1) codes for EPOS F (SEQ ID NO:8), a deduced protein with strong sequence similarities to cytochrome P450 oxygenases. EPOS F may take part in the adjustment of the redox state of the carbons C12, C5, and/or C3. The deduced protein product of *orf*14 (nucleotides 67334-68251 of SEQ ID NO:1), Orf 14 (SEQ ID NO:22) shows strong similarities to GI:3293544, a hypothetic protein with no proposed function from *Streptomyces coelicolor*, and also to GI:2654559, the human embrionic lung protein. It is also more distantly related to cation efflux system proteins like GI:2623026 from *Methanobacterium thermoautotrophicum*, so it might also take part in the export of epothilones from the producing cells. The remaining ORFs (*orf*6-*orf*13 and *orf*15) show no homologies to entries in the sequence databanks.

Example 13: Recombinant Expression of Epothilone Biosynthesis Genes

Epothilone synthase genes according to the present invention are expressed in heterologous organisms for the purposes of epothilone production at greater quantities than can be accomplished by fermentation of *Sorangium cellulosum*. A preferable host for heterologous expression is *Streptomyces*, e.g. *Streptomyces coelicolor*, which natively produces the polyketide actinorhodin. Techniques for recombinant PKS gene expression in this host are described in McDaniel *et al., Science* 262: 1546-1550 (1993) and Kao *et al., Science* 265: 509-512 (1994). See also, Holmes *et al., EMBO Journal* 12(8): 3183-3191 (1993) and Bibb *et al., Gene* 38: 215-226 (1985), as well as U.S. Patent Nos. 5,521,077, 5,672,491, and 5,712,146, which are incorporated herein by reference.

According to one method, the heterologous host strain is engineered to contain a chromosomal deletion of the actinorhodin (*act*) gene cluster. Expression plasmids containing the epothilone synthase genes of the invention are constructed by transferring DNA from a temperature-sensitive donor plasmid to a recipient shuttle vector in *E. coli* (McDaniel *et al.* (1993) and Kao *et al.* (1994)), such that the synthase genes are built-up by homologous recombination within the vector. Alternatively, the epothilone synthase gene cluster is introduced into the vector by restriction fragment ligation. Following selection, e.g. as described in Kao *et al.* (1994), DNA from the vector is introduced into the *act*-minus *Streptomyces coelicolor* strain according to protocols set forth in Hopwood *et al., Genetic Manipulation of* Streptomyces. *A Laboratory Manual* (John Innes Foundation, Norwich, United Kingdom, 1985), incorporated herein by reference. The recombinant *Streptomyces* strain is grown on R2YE medium (Hopwood *et al.* (1985)) and produces epothilones. Alternatively, the epothilone synthase genes according to the present invention are expressed in other host organisms such as pseudomonads, *Bacillus*, yeast, insect cells and/or *E. coli*. PKS and NRPS genes are preferably expressed in *E. coli* using the pT7-7 vector, which uses the T7 promoter. *See*, Tabor *et al., Proc. Natl. Acad. Sci. USA* 82: 1074-1078 (1985). In another embodiment, the expression vectors pKK223-3 and pKK223-2 are used to express PKS and NRPS genes in *E. coli*, either in transcriptional or translational fusion, behind the *tac or trc* promoter. Expression of PKS and NRPS genes in heterologous hosts, which do not naturally have the phosphopantetheinyl (P-pant) transferases needed for post-translational modification of PKS enzymes, requires the coexpression in the host of a P-pant transferase, as described by Kealey *et al., Proc. Natl. Acad. Sci. USA* 95: 505-509 (1998).

Example 14: Isolation of Epothilones from Producing Strains

Examples of cultivation, fermentation, and extraction procedures for polyketide isolation, which are useful for extracting epothilones from both native and recombinant hosts according to the present invention, are given in WO 93/10121, incorporated herein by reference, in Example 57 of U.S. Patent No. 5,639,949, in Gerth *et al.*, *J. Antibiotics* 49: 560-563 (1996), and in Swiss patent application no. 396/98, filed February 19, 1998, and U.S. patent application no. 09/248,910 (that discloses also preferred mutant strains of Sorangium cellulosum), both of which are incorporated herein by reference. The following are procedures that are useful for isolating epothilones from cultured *Sorangium cellulosum* strains such as So ce90, and may also be used for the isolation of epothilone from recombinant hosts.

A: Cultivation of epothilone-producing strains:

Strain: *Sorangium cellulosum* Soce-90 or a recombinant host strain according to the present invention.

Preservation of the strain: In liquid N_2.

Media: Precultures and intermediate cultures: G52
Main culture: 1B12

G52 Medium:

yeast extract, low in salt (BioSpringer, Maison Alfort, France)	2 g/l
$MgSO_4$ (7 H_2O)	1 g/l
$CaCl_2$ (2 H_2O)	1 g/l
soya meal defatted Soyamine 50T (Lucas Meyer, Hamburg, Germany)	2 g/l
potato starch Noredux A-150 (Blattmann, Waedenswil, Switzerland)	8 g/l
glucose anhydrous	2 g/l
EDTA-Fe(III)-Na salt (8 g/l)	1 ml/l

pH 7.4, corrected with KOH
Sterilisation: 20 mins. 120 °C

1B12 Medium:

potato starch Noredux A-150 (Blattmann, Waedenswil, Switzerland)	20 g/l
soya meal defatted Soyamine 50T (Lucas Meyer, Hamburg, Germany)	11 g/l
EDTA-Fe(III)-Na salt	8 mg/l

pH 7.8, corrected with KOH
Sterilisation: 20 mins. 120 °C

Addition of cyclodextrins and cyclodextrin derivatives:

Cyclodextrins (Fluka, Buchs, Switzerland, or Wacker Chemie, Munich, Germany) in different concentrations are sterilised separately and added to the 1B12 medium prior to seeding.

Cultivation: 1 ml of the suspension of *Sorangium cellulosum* Soce-90 from a liquid N_2 ampoule is transferred to 10 ml of G52 medium (in a 50 ml Erlenmeyer flask) and incubated for 3 days at 180 rpm in an agitator at 30°C, 25 mm displacement. 5 ml of this culture is added to 45 ml of G52 medium (in a 200 ml Erlenmeyer flask) and incubated for 3 days at 180 rpm in an agitator at 30°C, 25 mm displacement. 50 ml of this culture is then added to 450 ml of G52 medium (in a 2 litre Erlenmeyer flask) and incubated for 3 days at 180 rpm in an agitator at 30°C, 50 mm displacement.

Maintenance culture: The culture is overseeded every 3-4 days, by adding 50 ml of culture to 450 ml of G52 medium (in a 2 litre Erlenmeyer flask). All experiments and fermentations are carried out by starting with this maintenance culture.

Tests in a flask:

(I) Preculture in an agitating flask:

Starting with the 500 ml of maintenance culture, 1 x 450 ml of G52 medium are seeded with 50 ml of the maintenance culture and incubated for 4 days at 180 rpm in an agitator at 30°C, 50 mm displacement.

(ii) Main culture in the agitating flask:

40 ml of 1B12 medium plus 5 g/l 4-morpholine-propane-sulfonic acid (= MOPS) powder (in a 200 ml Erlenmeyer flask) are mixed with 5 ml of a 10x concentrated cyclodextrin solution, seeded with 10 ml of preculture and incubated for 5 days at 180 rpm in an agitator at 30°C, 50 mm displacement.

Fermentation: Fermentations are carried out on a scale of 10 litres, 100 litres and 500 litres. 20 litre and 100 litre fermentations serve as an intermediate culture step. Whereas the pre-cultures and intermediate cultures are seeded as the maintenance culture 10% (v/v), the main cultures are seeded with 20% (v/v) of the intermediate culture. Important: In contrast to the agitating cultures, the ingredients of the media for the fermentation are calculated on the final culture volume including the inoculum. If, for example, 18 litres of medium + 2 litres of inoculum are combined, then substances for 20 litres are weighed in, but are only mixed with 18 litres.

Preculture in an agitating flask:

Starting with the 500 ml maintenance culture, 4 x 450 ml of G52 medium (in a 2 litre Erlenmeyer flask) are each seeded with 50 ml thereof, and incubated for 4 days at 180 rpm in an agitator at 30°C, 50 mm displacement.

Intermediate culture, 20 litres or 100 litres:

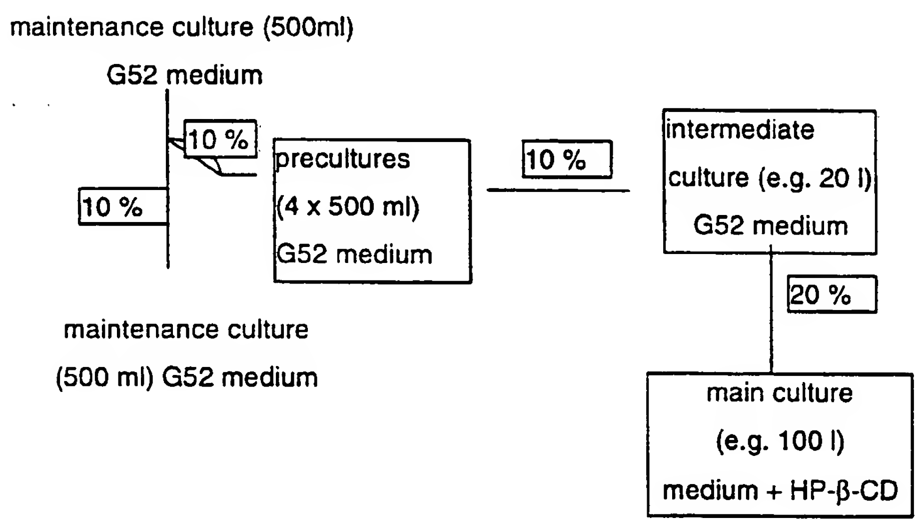
20 litres: 18 litres of G52 medium in a fermenter having a total volume of 30 litres are seeded with 2 litres of the preculture. Cultivation lasts for 3-4 days, and the conditions are: 30°C, 250 rpm, 0.5 litres of air per litre liquid per min, 0.5 bars excess pressure, no pH control.

100 litres: 90 litres of G52 medium in a fermenter having a total volume of 150 litres are seeded with 10 litres of the 20 litre intermediate culture. Cultivation lasts for 3-4 days, and the conditions are: 30°C, 150 rpm, 0.5 litres of air per litre liquid per min, 0.5 bars excess pressure, no pH control.

<u>Main culture, 10 litres, 100 litres or 500 litres:</u>

<u>10 litres:</u> The media substances for 10 litres of 1B12 medium are sterilised in 7 litres of water, then 1 litre of a sterile 10% 2-(hydroxypropyl) -β-cyclodextrin solution are added, and seeded with 2 litres of a 20 litre intermediate culture. The duration of the main culture is 6-7 days, and the conditions are: 30°C, 250 rpm, 0.5 litres of air per litre of liquid per min, 0.5 bars excess pressure, pH control with H_2SO_4/KOH to pH 7.6 +/- 0.5 (i.e. no control between pH 7.1 and 8.1).

<u>100 litres:</u> The media substances for 100 litres of 1B12 medium are sterilised in 70 litres of water, then 10 litres of a sterile 10% 2-(hydroxypropyl) -β-cyclodextrin solution are added, and seeded with 20 litres of a 20 litre intermediate culture. The duration of the main culture is 6-7 days, and the conditions are: 30°C, 200 rpm, 0.5 litres air per litre liquid per min., 0.5 bars excess pressure, pH control with H_2SO_4/KOH to pH 7.6 +/- 0.5. The chain of seeding for a 100 litre fermentation is shown schematically as follows:



<u>500 litres:</u> The media substances for 500 litres of 1B12 medium are sterilised in 350 litres of water, then 50 litres of a sterile 10% 2-(hydroxypropyl) -β-cyclodextrin solution are added, and seeded with 100 litres of a 100 litre intermediate culture. The duration of the main culture is 6-7 days, and the conditions are: 30°C, 120 rpm, 0.5 litres air per litre liquid per min., 0.5 bars excess pressure, pH control with H_2SO_4/KOH to pH 7.6 +/- 0.5.

<u>Product analysis:</u>

<u>Preparation of the sample:</u>

50 ml samples are mixed with 2 ml of polystyrene resin Amberlite XAD16 (Rohm + Haas, Frankfurt, Germany) and shaken at 180 rpm for one hour at 30°C. The resin is subsequently filtered using a 150 µm nylon sieve, washed with a little water and then added together with the filter to a 15 ml Nunc tube.

Elution of the product from the resin:

10 ml of isopropanol (>99%) are added to the tube with the filter and the resin. Afterwards, the sealed tube is shaken for 30 minutes at room temperature on a Rota-Mixer (Labinco BV, Netherlands). Then, 2 ml of the liquid are centrifuged off and the supernatant is added using a pipette to HPLC tubes.

HPLC analysis:

Column:	Waters-Symetry C18, 100 x 4 mm, 3.5 µm WAT066220 + preliminary column 3.9 x 20 mm WAT054225	
Solvents:	A: 0.02 % phosphoric acid	
	B: Acetonitrile (HPLC-Quality)	
Gradient:	41% B	from 0 to 7 min.
	100% B	from 7.2 to 7.8 min.
	41% B	from 8 to 12 min.
Oven temp.:	30°C	
Detection:	250 nm, UV-DAD detection	
Injection vol.:	10 µl	
Retention time:	Epo A: 4.30 min	Epo B: 5.38 min

B: Effect of the addition of cyclodextrin and cyclodextrin derivatives to the epothilone concentrations attained.

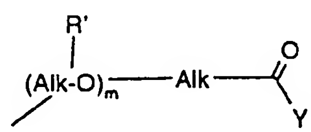
Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose with a relatively hydrophobic central cavity and a hydrophilic external surface area.

The following are distinguished in particular (the figures in parenthesis give the number of glucose units per molecule): α-cyclodextrin (6), β-cyclodextrin (7), γ- cyclodextrin (8), δ-cyclodextrin (9), ε- cyclodextrin (10), ζ-cyclodextrin (11), η-cyclodextrin (12), and θ-cyclodextrin (13). Especially preferred are δ-cyclodextrin and in particular α-cyclodextrin, β-cyclodextrin or γ-cyclodextrin, or mixtures thereof.

Cyclodextrin derivatives are primarily derivatives of the above-mentioned cyclodextrins, especially of α-cyclodextrin, β-cyclodextrin or γ-cyclodextrin, primarily those in which one or more up to all of the hydroxy groups (3 per glucose radical) are etherified or esterified. Ethers are primarily alkyl ethers, especially lower alkyl, such as methyl or ethyl ether, also propyl or butyl ether; the aryl-hydroxyalkyl ethers, such as phenyl-hydroxy-lower-alkyl, especially phenyl-hydroxyethyl ether; the hydroxyalkyl ethers, in particular hydroxy-lower-alkyl ethers, especially 2-hydroxyethyl, hydroxypropyl such as 2-hydroxypropyl or hydroxybutyl such as 2-hydroxybutyl ether; the carboxyalkyl ethers, in particular carboxy-lower-alkyl ethers, especially carboxymethyl or carboxyethyl ether; derivatised carboxyalkyl ethers, in particular derivatised carboxy-lower-alkyl ether in which the derivatised carboxy is etherified or amidated carboxy (primarily aminocarbonyl, mono- or di-lower-alkyl-aminocarbonyl, morpholino-, piperidino-, pyrrolidino- or piperazino-carbonyl, or alkyloxycarbonyl), in particular lower alkoxycarbonyl-lower-alkyl ether, for example methyloxycarbonylpropyl ether or ethyloxycarbonylpropyl ether; the sulfoalkyl ethers, in particular sulfo-lower-alkyl ethers, especially sulfobutyl ether; cyclodextrins in which one or more OH groups are etherified with a radical of formula

$$\text{-O-[alk-O-]}_n\text{-H}$$

wherein alk is alkyl, especially lower alkyl, and n is a whole number from 2 to 12, especially 2 to 5, in particular 2 or 3; cyclodextrins in which one or more OH groups are etherified with a radical of formula



wherein R' is hydrogen, hydroxy, -O-(alk-O)$_z$-H, -O-(alk(-R)-O-)$_p$-H or -O-(alk(-R)-O-)$_q$-alk-CO-Y; alk in all cases is alkyl, especially lower alkyl; m, n, p, q and z are a whole number from 1 to 12, preferably 1 to 5, in particular 1 to 3; and Y is OR_1 or NR_2R_3, wherein R_1, R_2 and R_3 independently of one another, are hydrogen or lower alkyl, or R_2 and R_3 combined together with the linking nitrogen signify morpholino, piperidino, pyrrolidino or piperazino;

or branched cyclodextrins, in which etherifications or acetals with other sugar molecules are present, especially glucosyl-, diglucosyl- (G_2-β-cyclodextrin), maltosyl- or dimaltosyl-cyclodextrin, or N-acetylglucosaminyl-, glucosaminyl-, N-acetylgalactosaminyl- or galactosaminyl-cyclodextrin.

Esters are primarily alkanoyl esters, in particular lower alkanoyl esters, such as acetyl esters of cyclodextrins.

It is also possible to have cyclodextrins in which two or more different said ether and ester groups are present at the same time.

Mixtures of two or more of the said cyclodextrins and/or cyclodextrin derivatives may also exist.

Preference is given in particular to α-, β- or γ-cyclodextrins or the lower alkyl ethers thereof, such as methyl-β-cyclodextrin or in particular 2,6-di-O-methyl-β-cyclodextrin, or in particular the hydroxy lower alkyl ethers thereof, such as 2-hydroxypropyl-α-, 2-hydroxy-propyl-β- or 2-hydroxypropyl-γ-cyclodextrin.

The cyclodextrins or cyclodextrin derivatives are added to the culture medium preferably in a concentration of 0.02 to 10, preferably 0.05 to 5, especially 0.1 to 4, for example 0.1 to 2 percent by weight (w/v).

Cyclodextrins or cyclodextrin derivatives are known or may be produced by known processes (see for example US 3,459,731; US 4,383,992; US 4,535,152; US 4,659,696; EP 0 094 157; EP 0 149 197; EP 0 197 571; EP 0 300 526; EP 0 320 032; EP 0 499 322; EP 0 503 710; EP 0 818 469; WO 90/12035; WO 91/11200; WO 93/19061; WO 95/08993; WO 96/14090; GB 2,189,245; DE 3,118,218; DE 3,317,064 and the references mentioned therein, which also refer to the synthesis of cyclodextrins or cyclodextrin derivatives, or also: T. Loftsson and M.E. Brewster (1996): Pharmaceutical Applications of Cyclodextrins: Drug Solubilization and Stabilisation: Journal of Pharmaceutical Science 85 (10):1017-1025; R.A. Rajewski and V.J. Stella(1996): Pharmaceutical Applications of Cyclodextrins: In Vivo Drug Delivery: Journal of Pharmaceutical Science 85 (11): 1142-1169).

All the cyclodextrin derivatives tested here are obtainable from the company Fluka, Buchs, CH. The tests are carried out in 200 ml agitating flasks with 50 ml culture volume. As controls, flasks with adsorber resin Amberlite XAD-16 (Rohm & Haas, Frankfurt, Germany) and without any adsorber addition are used. After incubation for 5 days, the following epothilone titres can be determined by HPLC:

Table 2:

Addition	order No.	Conc [%w/v][1]	Epo A [mg/l]	Epo B [mg/l]
Amberlite XAD-16 (v/v)		**2.0 (%v/v)**	**9.2**	**3.8**

Addition	order No.	Conc [%w/v][1]	Epo A [mg/l]	Epo B [mg/l]
2-hydroxypropyl-β-cyclodextrin	56332	0.1	2.7	1.7
2-hydroxypropyl-β-cyclodextrin	"	0.5	4.7	3.3
2-hydroxypropyl-β-cyclodextrin	"	1.0	4.7	3.4
2-hydroxypropyl-β-cyclodextrin	"	2.0	4.7	4.1
2-hydroxypropyl-β-cyclodextrin	"	5.0	1.7	0.5
2-hydroxypropyl- α-cyclodextrin	56330	0.5	1.2	1.2
2-hydroxypropyl- α-cyclodextrin	"	1.0	1.2	1.2
2-hydroxypropyl- α-cyclodextrin	"	5.0	2.5	2.3
β-cyclodextrin	28707	0.1	1.6	1.3
β-cyclodextrin	"	0.5	3.6	2.5
β-cyclodextrin	"	1.0	4.8	3.7
β-cyclodextrin	"	2.0	4.8	2.9
β-cyclodextrin	"	5.0	1.1	0.4
methyl-β-cyclodextrin	66292	0.5	0.8	<0.3
methyl-β-cyclodextrin	"	1.0	<0.3	<0.3
methyl-β-cyclodextrin	"	2.0	<0.3	<0.3
2,6 di-o-methyl-β-cyclodextrin	39915	1.0	<0.3	<0.3
2-hydroxypropyl-γ-cyclodextrin	56334	0.1	0.3	<0.3
2-hydroxypropyl-γ-cyclodextrin	"	0.5	0.9	0.8
2-hydroxypropyl-γ-cyclodextrin	"	1.0	1.1	0.7
2-hydroxypropyl-γ-cyclodextrin	"	2.0	2.6	0.7
2-hydroxypropyl-γ-cyclodextrin	"	5.0	5.0	1.1
no addition			**0.5**	**0.5**

[1]) Apart from Amberlite (%v/v), all percentages are by weight (%w/v).

Few of the cyclodextrins tested (2,6-di-o-methyl-β-cyclodextrin, methyl-β-cyclodextrin) display no effect or a negative effect on epothilone production at the concentrations used. 1-2% 2-hydroxy-propyl-β-cyclodextrin and β-cyclodextrin increase epothilone production in the examples by 6 to 8 times compared with production using no cyclodextrins.

C: 10 litre fermentation with 1% 2-(hydroxypropyl)-β-cyclodextrin):

Fermentation is carried out in a 15 litre glass fermenter. The medium contains 10 g/l of 2-(hydroxypropyl)-β-cyclodextrin from Wacker Chemie, Munich, Germany. The progress of fermentation is illustrated in Table 3. Fermentation is ended after 6 days and working up takes place.

Table 3: Progress of a 10 litre fermentation

duration of culture [d]	Epothilone A [mg/l]	Epothilone B [mg/l]
0	0	0
1	0	0
2	0.5	0.3
3	1.8	2.5
4	3.0	5.1
5	3.7	5.9
6	3.6	5.7

D: 100 litre fermentation with 1% 2-(hydroxypropyl)-β-cyclodextrin):

Fermentation is carried out in a 150 litre fermenter. The medium contains 10 g/l of 2-(Hydroxypropyl)-β-cyclodextrin. The progress of fermentation is illustrated in Table 4. The fermentation is harvested after 7 days and worked up.

Table 4: Progress of a 100 litre fermentation

duration of culture [d]	Epothilone A [mg/l]	Epothilone B [mg/l]
0	0	0
1	0	0
2	0.3	0

3	0.9	1.1
4	1.5	2.3
5	1.6	3.3
6	1.8	3.7
7	1.8	3.5

E: 500 litre fermentation with 1% 2-(hydroxypropyl)-β-cyclodextrin):

Fermentation is carried out in a 750 litre fermenter. The medium contains 10 g/l of 2-(Hydroxypropyl)-β-cyclodextrin. The progress of fermentation is illustrated in Table 5. The fermentation is harvested after 7 days and worked up.

Table 5: Progress of a 500 litre fermentation

duration of culture [d]	Epothilone A [mg/l]	Epothilone B [mg/l]
0	0	0
1	0	0
2	0	0
3	0.6	0.6
4	1.7	2.2
5	3.1	4.5
6	3.1	5.1

F: Comparison example 10 litre fermentation without adding an adsorber:

Fermentation is carried out in a 15 litre glass fermenter. The medium does not contain any cyclodextrin or other adsorber. The progress of fermentation is illustrated in Table 6. The fermentation is not harvested and worked up.

Table 6: Progress of a 10 litre fermentation without adsorber.

duration of culture [d]	Epothilone A [mg/l]	Epothilone B [mg/l]
0	0	0
1	0	0
2	0	0
3	0	0
4	0.7	0.7
5	0.7	1.0
6	0.8	1.3

G: Working up of the epothilones: Isolation from a 500 litre main culture:

The volume of harvest from the 500 litre main culture of example 2D is 450 litres and is separated using a Westfalia clarifying separator Type SA-20-06 (rpm = 6500) into the liquid phase (centrifugate + rinsing water = 650 litres) and solid phase (cells = ca. 15 kg). The main part of the epothilones are found in the centrifugate, The centrifuged cell pulp contains < 15% of the determined epothilone portion and is not further processed. The 650 litre centrifugate is then placed in a 4000 litre stirring vessel, mixed with 10 litres of Amberlite XAD-16 (centrifugate:resin volume = 65:1) and stirred. After a period of contact of ca. 2 hours, the resin is centrifuged away in a Heine overflow centrifuge (basket content 40 litres; rpm = 2800). The resin is discharged from the centrifuge and washed with 10-15 litres of deionised water. Desorption is effected by stirring the resin twice, each time in portions with 30 litres of isopropanol in 30 litre glass stirring vessels for 30 minutes. Separation of the isopropanol phase from the resin takes place using a suction filter. The isopropanol is then removed from the combined isopropanol phases by adding 15-20 litres of water in a vacuum-operated circulating evaporator (Schmid-Verdampfer) and the resulting water phase of ca. 10 litres is extracted 3x each time with 10 litres of ethyl acetate. Extraction is effected in 30 litre glass stirring vessels. The ethyl acetate extract is concentrated to 3-5 litres in a vacuum-operated circulating evaporator (Schmid-Verdampfer) and afterwards concentrated to dryness in a rotary evaporator (Büchi type) under vacuum. The result is an ethyl acetate extract of 50.2 g. The ethyl acetate extract is dissolved in

500 ml of methanol, the insoluble portions filtered off using a folded filter, and the solution added to a 10 kg Sephadex LH 20 column (Pharmacia, Uppsala, Sweden) (column diameter 20 cm, filling level ca. 1.2 m). Elution is effected with methanol as eluant. Epothilone A and B is present predominantly in fractions 21-23 (at a fraction size of 1 litre). These fractions are concentrated to dryness in a vacuum on a rotary evaporator (total weight 9.0 g). These Sephadex peak fractions (9.0 g) are thereafter dissolved in 92 ml of acetonitrile:-water:-methylene chloride = 50:40:2, the solution filtered through a folded filter and added to a RP column (equipment Prepbar 200, Merck; 2. 0 kg LiChrospher RP-18 Merck, grain size 12µm, column diameter 10 cm, filling level 42 cm; Merck, Darmstadt, Germany). Elution is effected with acetonitrile:water = 3:7 (flow rate = 500 ml/min.; retention time of epothilone A = ca. 51-59 mins.; retention time of epothilone B = ca. 60-69 mins.). Fractionation is monitored with a UV detector at 250 nm. The fractions are concentrated to dryness under vacuum on a Büchi-Rotavapor rotary evaporator. The weight of the epothilone A peak fraction is 700 mg, and according to HPLC (external standard) it has a content of 75.1%. That of the epothilone B peak fraction is 1980 mg, and the content according to HPLC (external standard) is 86.6%. Finally, the epothilone A fraction (700 mg) is crystallised from 5 ml of ethyl acetate:toluene = 2:3, and yields 170 mg of epothilone A pure crystallisate [content according to HLPC (% of area) = 94.3%]. Crystallisation of the epothilone B fraction (1980 mg) is effected from 18 ml of methanol and yields 1440 mg of epothilone B pure crystallisate [content according to HPLC (% of area) = 99.2%]. m.p. (Epothilone B): e.g. 124-125 °C; ^{1}H-NMR data for Epothilone B:

500 MHz-NMR, solvent: DMSO-d6. Chemical displacement δ in ppm relative to TMS. s = singlet; d = doublet; m = multiplet

δ (Multiplicity)	Integral (number of H)
7.34 (s)	1
6.50 (s)	1
5.28 (d)	1
5.08 (d)	1
4.46 (d)	1
4.08 (m)	1

3.47 (m)	1
3.11 (m)	1
2.83 (dd)	1
2.64 (s)	3
2.36 (m)	2
2.09 (s)	3
2.04 (m)	1
1.83 (m)	1
1.61 (m)	1
1.47 - 1.24 (m)	4
1.18 (s)	6
1.13 (m)	2
1.06 (d)	3
0.89 (d + s, overlapping)	6
	$\Sigma = 41$

Example 15: Medical Uses of Recombinantly Produced Epothilones

Pharmaceutical preparations or compositions comprising epothilones are used for example in the treatment of cancerous diseases, such as various human solid tumors. Such anticancer formulations comprise, for example, an active amount of an epothilone together with one or more organic or inorganic, liquid or solid, pharmaceutically suitable carrier materials. Such formulations are delivered, for example, enterally, nasally, rectally, orally, or parenterally, particularly intramuscularly or intravenously. The dosage of the active ingredient is dependent upon the weight, age, and physical and pharmacokinetical condition of the patient and is further dependent upon the method of delivery. Because epothilones mimic the biological effects of taxol, epothilones may be substituted for taxol in compositions and methods utilizing taxol in the treatment of cancer. *See*, for example, U.S.

Patent Nos. 5,496,804, 5,565,478, and 5,641,803, all of which are incorporated herein by reference.

For example, for treatments, epothilone B is supplied in individual 2 ml glass vials formulated as 1 mg/1 ml of clear, colorless intravenous concentrate. The substance is formulated in polyethylene glycol 300 (PEG 300) and diluted with 50 or 100 ml 0.9% Sodium Chloride Injection, USP, to achieve the desired final concentration of the drug for infusion. It is administered as a single 30-minute intravenous infusion every 21 days (treatment three-weekly) for six cycles, or as a single 30-minute intravenous infusion every 7 days (weekly treatment).

Preferably, for weekly treatment, the dose is between about 0.1 and about 6, preferably about 0.1 and about 5 mg/m^2, more preferably about 0.1 and about 3 mg/m^2, even more preferably 0.1 and 1.7 mg/m^2, most preferably about 0.3 and about 1 mg/m^2; for three-weekly treatment (treatment every three weeks or every third week) the dose is between about 0.3 and about 18 mg/m^2, preferably about 0.3 and about 15 mg/m^2, more preferably about 0.3 and about 12 mg/m^2, even more preferably about 0.3 and about 7.5 mg/m^2, still more preferably about 0.3 and about 5 mg/m^2, most preferably about 1.0 and about 3.0 mg/m^2. This dose is preferably administered to the human by intravenous (i.v.) administration during 2 to 180 min, preferably 2 to 120 min, more preferably during about 5 to about 30 min, most preferably during about 10 to about 30 min, e.g. during about 30 min.

While the present invention has been described with reference to specific embodiments thereof, it will be appreciated that numerous variations, modifications, and embodiments are possible, and accordingly, all such variations, modifications and embodiments are to be regarded as being within the spirit and scope of the present invention.

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSE OF PATENT PROCEDURES

INTERNATIONAL FORM

TO
Novartis AG
Novartis Corporation
Patent and Trademark Dept.
3054 Cornwallis Rd.
Research Triangle Park, NC 27709

NAME AND ADDRESS
OF DEPOSITOR

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
Escherichia coli DH10B (pEP015)	NRRL B-30033

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on June 11, 1998(date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I. above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: Agricultural Research Culture Collection (NRRL) International Depositary Authority	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): [signature]
Address: 1815 N. University Street Peoria, Illinois 61604 U.S.A.	Date: 7-21-98

[1] Where Rule 6.4(d) applies, such date is the date on which the status of international depositary authority was acquired.

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSE OF PATENT PROCEDURES

INTERNATIONAL FORM

TO
Novatis AG
c/o Novartis Agricultural Biotechnology
Research, Inc.
Patent & Trademark Department
3054 Cornwallis Road
Research Triangle Park, NC 27709
NAME AND ADDRESS
OF DEPOSITOR

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM	
Identification reference given by the DEPOSITOR: Escherichia coli DH10B [pEPO32]	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NRRL B-30119

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on April 16, 1999 (date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I. above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: Agricultural Research Culture Collection (NRRL) International Depositary Authority Address: 1815 N. University Street Peoria, Illinois 61604 U.S.A.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): Date: 5-24-99

[1] Where Rule 6.4(d) applies, such date is the date on which the status of international depositary authority was acquired.

What is claimed is:

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes at least one polypeptide involved in the biosynthesis of epothilone.

2. An isolated nucleic acid molecule according to claim 1, wherein said nucleotide sequence is isolated from a myxobacterium.

3. An isolated nucleic acid molecule according to claim 2, wherein said myxobacterium is *Sorangium cellulosum.*

4. A chimeric gene comprising a heterologous promoter sequence operatively linked to a nucleic acid molecule according to claim 1.

5. A recombinant vector comprising a chimeric gene according to claim 4.

6. A recombinant host cell comprising a chimeric gene according to claim 4.

7. The recombinant host cell of claim 6, which is a bacteria.

8. The recombinant host cell of claim 7, which is an Actinomycete.

9. The recombinant host cell of claim 8, which is *Streptomyces.*

10. A Bac clone comprising a nucleic acid molecule according to claim 1.

11. The Bac clone of claim 10, which is pEPO15.

12. An isolated nucleic acid molecule according to claim 1, wherein said polypeptide comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: SEQ ID NO:2, amino acids 11-437 of SEQ ID NO:2, amino acids 543-864 of SEQ ID NO:2, amino acids 974-1273 of SEQ ID NO:2, amino acids 1314-1385 of SEQ ID NO:2, SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids

118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, amino acids 1344-1351 of SEQ ID NO:3, SEQ ID NO:4, amino acids 7-432 of SEQ ID NO:4, amino acids 539-859 of SEQ ID NO:4, amino acids 869-1037 of SEQ ID NO:4, amino acids 1439-1684 of SEQ ID NO:4, amino acids 1722-1792 of SEQ ID NO:4, SEQ ID NO:5, amino acids 39-457 of SEQ ID NO:5, amino acids 563-884 of SEQ ID NO:5, amino acids 1147-1399 of SEQ ID NO:5, amino acids 1434-1506 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 3886-4048 of SEQ ID NO:5, amino acids 4433-4719 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, SEQ ID NO:6, amino acids 35-454 of SEQ ID NO:6, amino acids 561-881 of SEQ ID NO:6, amino acids 1143-1393 of SEQ ID NO:6, amino acids 1430-1503 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, amino acids 2053-2373 of SEQ ID NO:6, amino acids 2383-2551 of SEQ ID NO:6, amino acids 2671-3045 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, SEQ ID NO:7, amino acids 32-450 of SEQ ID NO:7, amino acids 556-877 of SEQ ID NO:7, amino acids 887-1051 of SEQ ID NO:7, amino acids 1478-1790 of SEQ ID NO:7, amino acids 1810-2055 of SEQ ID NO:7, amino acids 2093-2164 of SEQ ID NO:7, amino acids 2165-2439 of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:22.

13. An isolated nucleic acid molecule according to claim 12, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:2, amino acids 11-437 of SEQ ID NO:2, amino acids 543-864 of SEQ ID NO:2, amino acids 974-1273 of SEQ ID NO:2, amino acids 1314-1385 of SEQ ID NO:2, SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino

acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, amino acids 1344-1351 of SEQ ID NO:3, SEQ ID NO:4, amino acids 7-432 of SEQ ID NO:4, amino acids 539-859 of SEQ ID NO:4, amino acids 869-1037 of SEQ ID NO:4, amino acids 1439-1684 of SEQ ID NO:4, amino acids 1722-1792 of SEQ ID NO:4, SEQ ID NO:5, amino acids 39-457 of SEQ ID NO:5, amino acids 563-884 of SEQ ID NO:5, amino acids 1147-1399 of SEQ ID NO:5, amino acids 1434-1506 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 3886-4048 of SEQ ID NO:5, amino acids 4433-4719 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, SEQ ID NO:6, amino acids 35-454 of SEQ ID NO:6, amino acids 561-881 of SEQ ID NO:6, amino acids 1143-1393 of SEQ ID NO:6, amino acids 1430-1503 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, amino acids 2053-2373 of SEQ ID NO:6, amino acids 2383-2551 of SEQ ID NO:6, amino acids 2671-3045 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, SEQ ID NO:7, amino acids 32-450 of SEQ ID NO:7, amino acids 556-877 of SEQ ID NO:7, amino acids 887-1051 of SEQ ID NO:7, amino acids 1478-1790 of SEQ ID NO:7, amino acids 1810-2055 of SEQ ID NO:7, amino acids 2093-2164 of SEQ ID NO:7, amino acids 2165-2439 of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:22.

14. An isolated nucleic acid molecule according to claim 12, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: the complement of nucleotides 1900-3171 of SEQ ID NO:1, nucleotides 3415-5556 of SEQ ID NO:1, nucleotides 7610-11875 of SEQ ID NO:1, nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 10529-11428 of SEQ

ID NO:1, nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, nucleotides 15901-15924 of SEQ ID NO:1, nucleotides 16251-21749 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 21746-43519 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 43524-54920 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, nucleotides 51534-52657 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, nucleotides 54935-62254 of SEQ ID NO:1, nucleotides 55028-56284 of SEQ ID NO:1, nucleotides 56600-57565 of SEQ ID NO:1, nucleotides 57593-58087 of SEQ ID NO:1, nucleotides 59366-60304 of SEQ ID NO:1, nucleotides 60362-61099 of SEQ ID NO:1, nucleotides 61211-61426 of SEQ ID NO:1, nucleotides 61427-62254 of SEQ ID NO:1, nucleotides 62369-63628 of SEQ ID NO:1, nucleotides 67334-68251 of SEQ ID NO:1, and nucleotides 1-68750 SEQ ID NO:1.

15. A nucleic acid molecule according to claim 12, wherein said nucleotide sequence is selected from the group consisting of: the complement of nucleotides 1900-3171 of SEQ ID NO:1, nucleotides 3415-5556 of SEQ ID NO:1, nucleotides 7610-11875 of SEQ ID NO:1, nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, nucleotides 15901-15924 of SEQ ID NO:1, nucleotides 16251-21749 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 21746-43519 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 43524-54920 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, nucleotides 51534-52657 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID

NO:1, nucleotides 54935-62254 of SEQ ID NO:1, nucleotides 55028-56284 of SEQ ID NO:1, nucleotides 56600-57565 of SEQ ID NO:1, nucleotides 57593-58087 of SEQ ID NO:1, nucleotides 59366-60304 of SEQ ID NO:1, nucleotides 60362-61099 of SEQ ID NO:1, nucleotides 61211-61426 of SEQ ID NO:1, nucleotides 61427-62254 of SEQ ID NO:1, nucleotides 62369-63628 of SEQ ID NO:1, nucleotides 67334-68251 of SEQ ID NO:1, and nucleotides 1-68750 SEQ ID NO:1.

16. A chimeric gene comprising a heterologous promoter sequence operatively linked to a nucleic acid molecule according to claim 12.

17. A recombinant vector comprising a chimeric gene according to claim 16.

18. A recombinant host cell comprising a chimeric gene according to claim 16.

19. The recombinant host cell of claim 18, which is a bacteria.

20. The recombinant host cell of claim 19, which is an Actinomycete.

21. The recombinant host cell of claim 20, which is *Streptomyces.*

22. An isolated nucleic acid molecule according to claim 1, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: the complement of nucleotides 1900-3171 of SEQ ID NO:1, nucleotides 3415-5556 of SEQ ID NO:1, nucleotides 7610-11875 of SEQ ID NO:1, nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID

NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, nucleotides 15901-15924 of SEQ ID NO:1, nucleotides 16251-21749 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 21746-43519 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 43524-54920 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, nucleotides 51534-52657 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, nucleotides 54935-62254 of SEQ ID NO:1, nucleotides 55028-56284 of SEQ ID NO:1, nucleotides 56600-57565 of SEQ ID NO:1, nucleotides 57593-58087 of SEQ ID NO:1, nucleotides 59366-60304 of SEQ ID NO:1, nucleotides 60362-61099 of SEQ ID NO:1, nucleotides 61211-61426 of SEQ ID NO:1, nucleotides 61427-62254 of SEQ ID NO:1, nucleotides 62369-63628 of SEQ ID NO:1, nucleotides 67334-68251 of SEQ ID NO:1, and nucleotides 1-68750 SEQ ID NO:1.

23. A chimeric gene comprising a heterologous promoter sequence operatively linked to a nucleic acid molecule according to claim 22.

24. A recombinant vector comprising a chimeric gene according to claim 23.

25. A recombinant host cell comprising a chimeric gene according to claim 23.

26. The recombinant host cell of claim 25, which is a bacteria.

27. The recombinant host cell of claim 26, which is an Actinomycete.

28. The recombinant host cell of claim 27, which is *Streptomyces*.

29. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes at least one epothilone synthase domain.

30. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is a β-ketoacyl-synthase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7.

31. An isolated nucleic acid molecule according to claim 30, wherein said β-ketoacyl-synthase domain comprises an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7.

32. An isolated nucleic acid molecule according to claim 30, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, and nucleotides 55028-56284 of SEQ ID NO:1.

33. An isolated nucleic acid molecule according to claim 30, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, and nucleotides 55028-56284 of SEQ ID NO:1.

34. An isolated nucleic acid molecule according to claim 30, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 7643-8920 of SEQ ID NO:1, nucleotides 16269-17546 of SEQ ID NO:1, nucleotides 21860-23116 of SEQ ID NO:1, nucleotides 26318-27595 of SEQ ID NO:1, nucleotides 30815-32092 of SEQ ID NO:1, nucleotides 37052-38320 of SEQ ID NO:1, nucleotides 43626-44885 of SEQ ID NO:1, nucleotides 48087-49361 of SEQ ID NO:1, and nucleotides 55028-56284 of SEQ ID NO:1.

35. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is a an acyltransferase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7.

36. An isolated nucleic acid molecule according to claim 35, wherein said acyltransferase domain comprises an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7.

37. An isolated nucleic acid molecule according to claim 35, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, and nucleotides 56600-57565 of SEQ ID NO:1.

38. An isolated nucleic acid molecule according to claim 35, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, and nucleotides 56600-57565 of SEQ ID NO:1.

39. An isolated nucleic acid molecule according to claim 35, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 9236-10201 of SEQ ID NO:1, nucleotides 17865-18827 of SEQ ID NO:1, nucleotides 23431-24397 of SEQ ID NO:1, nucleotides 27911-28876 of SEQ ID NO:1, nucleotides 32408-33373 of SEQ ID NO:1, nucleotides 38636-39598 of SEQ ID NO:1, nucleotides 45204-46166 of SEQ ID NO:1, nucleotides 49680-50642 of SEQ ID NO:1, and nucleotides 56600-57565 of SEQ ID NO:1.

40. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is an enoyl reductase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7.

41. An isolated nucleic acid molecule according to claim 40, wherein said enoyl reductase domain comprises an amino acid sequence selected from the group consisting

of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7.

42. An isolated nucleic acid molecule according to claim 40, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, and nucleotides 59366-60304 of SEQ ID NO:1.

43. An isolated nucleic acid molecule according to claim 40, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, and nucleotides 59366-60304 of SEQ ID NO:1.

44. An isolated nucleic acid molecule according to claim 40, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 10529-11428 of SEQ ID NO:1, nucleotides 35042-35902 of SEQ ID NO:1, nucleotides 41369-42256 of SEQ ID NO:1, and nucleotides 59366-60304 of SEQ ID NO:1.

45. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is an acyl carrier protein domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7.

46. An isolated nucleic acid molecule according to claim 45, wherein said acyl carrier protein domain comprises an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID

NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7.

47. An isolated nucleic acid molecule according to claim 45, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, and nucleotides 61211-61426 of SEQ ID NO:1.

48. An isolated nucleic acid molecule according to claim 45, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, and nucleotides 61211-61426 of SEQ ID NO:1.

49. An isolated nucleic acid molecule according to claim 45, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 11549-11764 of SEQ ID NO:1, nucleotides 21414-21626 of SEQ ID NO:1, nucleotides 26045-26263 of SEQ ID NO:1, nucleotides 30539-30759 of SEQ ID NO:1, nucleotides 36773-36991 of SEQ ID NO:1, nucleotides 43163-43378 of SEQ ID NO:1, nucleotides 47811-48032 of SEQ ID NO:1, nucleotides 54540-54758 of SEQ ID NO:1, and nucleotides 61211-61426 of SEQ ID NO:1.

50. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is a dehydratase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of:

amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7.

51. An isolated nucleic acid molecule according to claim 50, wherein said dehydratase domain comprises an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7.

52. An isolated nucleic acid molecule according to claim 50, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, and nucleotides 57593-58087 of SEQ ID NO:1.

53. An isolated nucleic acid molecule according to claim 50, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, and nucleotides 57593-58087 of SEQ ID NO:1.

54. An isolated nucleic acid molecule according to claim 50, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 18855-19361 of SEQ ID NO:1, nucleotides 33401-33889 of SEQ ID NO:1, nucleotides 39635-40141 of SEQ ID NO:1, nucleotides 50670-51176 of SEQ ID NO:1, and nucleotides 57593-58087 of SEQ ID NO:1.

55. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is a β-ketoreductase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino

acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7.

56. An isolated nucleic acid molecule according to claim 55, wherein said β-ketoreductase domain comprises an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7.

57. An isolated nucleic acid molecule according to claim 55, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, and nucleotides 60362-61099 of SEQ ID NO:1.

58. An isolated nucleic acid molecule according to claim 55, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, and nucleotides 60362-61099 of SEQ ID NO:1.

59. An isolated nucleic acid molecule according to claim 55, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 20565-21302 of SEQ ID NO:1, nucleotides 25184-25942 of SEQ ID NO:1, nucleotides 29678-30429 of SEQ ID NO:1, nucleotides 35930-36667 of SEQ ID NO:1, nucleotides 42314-43048 of SEQ ID

NO:1, nucleotides 46950-47702 of SEQ ID NO:1, nucleotides 53697-54431 of SEQ ID NO:1, and nucleotides 60362-61099 of SEQ ID NO:1.

60. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is a methyltransferase domain comprising an amino acid sequence substantially similar to amino acids 2671-3045 of SEQ ID NO:6.

61. An isolated nucleic acid molecule according to claim 60, wherein said methyltransferase domain comprises amino acids 2671-3045 of SEQ ID NO:6.

62. An isolated nucleic acid molecule according to claim 60, wherein said nucleotide sequence is substantially similar to nucleotides 51534-52657 of SEQ ID NO:1.

63. An isolated nucleic acid molecule according to claim 60, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of nucleotides 51534-52657 of SEQ ID NO:1.

64. An isolated nucleic acid molecule according to claim 60, wherein said nucleotide sequence is nucleotides 51534-52657 of SEQ ID NO:1.

65. An isolated nucleic acid molecule according to claim 29, wherein said epothilone synthase domain is a thioesterase domain comprising an amino acid sequence substantially similar to amino acids 2165-2439 of SEQ ID NO:7.

66. An isolated nucleic acid molecule according to claim 65, wherein said thioesterase domain comprises amino acids 2165-2439 of SEQ ID NO:7.

67. An isolated nucleic acid molecule according to claim 65, wherein said nucleotide sequence is substantially similar to nucleotides 61427-62254 of SEQ ID NO:1.

68. An isolated nucleic acid molecule according to claim 65, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of nucleotides 61427-62254 of SEQ ID NO:1.

69. An isolated nucleic acid molecule according to claim 65, wherein said nucleotide sequence is nucleotides 61427-62254 of SEQ ID NO:1.

70. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a non-ribosomal peptide synthetase, wherein said non-ribosomal peptide synthetase comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, and amino acids 1344-1351 of SEQ ID NO:3.

71. An isolated nucleic acid molecule according to claim 70, wherein said non-ribosomal peptide synthetase comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:3, amino acids 72-81 of SEQ ID NO:3, amino acids 118-125 of SEQ ID NO:3, amino acids 199-212 of SEQ ID NO:3, amino acids 353-363 of SEQ ID NO:3, amino acids 549-565 of SEQ ID NO:3, amino acids 588-603 of SEQ ID NO:3, amino acids 669-684 of SEQ ID NO:3, amino acids 815-821 of SEQ ID NO:3, amino acids 868-892 of SEQ ID NO:3, amino acids 903-912 of SEQ ID NO:3, amino acids 918-940 of SEQ ID NO:3, amino acids 1268-1274 of SEQ ID NO:3, amino acids 1285-1297 of SEQ ID NO:3, amino acids 973-1256 of SEQ ID NO:3, and amino acids 1344-1351 of SEQ ID NO:3.

72. An isolated nucleic acid molecule according to claim 70, wherein said nucleotide sequence is substantially similar to a nucleotide sequence selected from the group consisting of: nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID

NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, and nucleotides 15901-15924 of SEQ ID NO:1.

73. An isolated nucleic acid molecule according to claim 70, wherein said nucleotide sequence comprises a consecutive 20 base pair nucleotide portion identical in sequence to a consecutive 20 base pair portion of a nucleotide sequence selected from the group consisting of: nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, and nucleotides 15901-15924 of SEQ ID NO:1.

74. An isolated nucleic acid molecule according to claim 70, wherein said nucleotide sequence is selected from the group consisting of: nucleotides 11872-16104 of SEQ ID NO:1, nucleotides 12085-12114 of SEQ ID NO:1, nucleotides 12223-12246 of SEQ ID NO:1, nucleotides 12466-12507 of SEQ ID NO:1, nucleotides 12928-12960 of SEQ ID NO:1, nucleotides 13516-13566 of SEQ ID NO:1, nucleotides 13633-13680 of SEQ ID NO:1, nucleotides 13876-13923 of SEQ ID NO:1, nucleotides 14313-14334 of SEQ ID NO:1, nucleotides 14473-14547 of SEQ ID NO:1, nucleotides 14578-14607 of SEQ ID NO:1, nucleotides 14623-14692 of SEQ ID NO:1, nucleotides 15673-15693 of SEQ ID NO:1, nucleotides 15724-15762 of SEQ ID NO:1, nucleotides 14788-15639 of SEQ ID NO:1, and nucleotides 15901-15924 of SEQ ID NO:1.

75. A method for heterologous expression of epothilone in a recombinant host, comprising:

(a) introducing a chimeric gene according to claim 4 into a host; and

(b) growing the host in conditions that allow biosynthesis of epothilone in the host.

76. A method for producing epothilone, comprising:

(a) expressing epothilone in a recombinant host by the method of claim 75; and

(b) extracting epothilone from the recombinant host.

77. An isolated polypeptide comprising an amino acid sequence that consists of an epothilone synthase domain.

78. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is a β-ketoacyl-synthase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7.

79. An isolated polypeptide according to claim 78, wherein said β-ketoacyl-synthase domain comprises an amino acid sequence selected from the group consisting of: amino acids 11-437 of SEQ ID NO:2, amino acids 7-432 of SEQ ID NO:4, amino acids 39-457 of SEQ ID NO:5, amino acids 1524-1950 of SEQ ID NO:5, amino acids 3024-3449 of SEQ ID NO:5, amino acids 5103-5525 of SEQ ID NO:5, amino acids 35-454 of SEQ ID NO:6, amino acids 1522-1946 of SEQ ID NO: 6, and amino acids 32-450 of SEQ ID NO:7.

80. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is an acyltransferase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7.

81. An isolated polypeptide according to claim 80, wherein said acyltransferase domain comprises an amino acid sequence selected from the group consisting of: amino

acids 543-864 of SEQ ID NO:2, amino acids 539-859 of SEQ ID NO:4, amino acids 563-884 of SEQ ID NO:5, amino acids 2056-2377 of SEQ ID NO:5, amino acids 3555-3876 of SEQ ID NO:5, amino acids 5631-5951 of SEQ ID NO:5, amino acids 561-881 of SEQ ID NO:6, amino acids 2053-2373 of SEQ ID NO:6, and amino acids 556-877 of SEQ ID NO:7.

82. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is an enoyl reductase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7.

83. An isolated polypeptide according to claim 82, wherein said enoyl reductase domain comprises an amino acid sequence selected from the group consisting of: amino acids 974-1273 of SEQ ID NO:2, amino acids 4433-4719 of SEQ ID NO:5, amino acids 6542-6837 of SEQ ID NO:5, and amino acids 1478-1790 of SEQ ID NO:7.

84. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is an acyl carrier protein domain, wherein said polypeptide comprises an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7.

85. An isolated polypeptide according to claim 84, wherein said acyl carrier protein domain comprises an amino acid sequence selected from the group consisting of: amino acids 1314-1385 of SEQ ID NO:2, amino acids 1722-1792 of SEQ ID NO:4, amino acids 1434-1506 of SEQ ID NO:5, amino acids 2932-3005 of SEQ ID NO:5, amino acids 5010-5082 of SEQ ID NO:5, amino acids 7140-7211 of SEQ ID NO:5, amino acids 1430-1503 of SEQ ID NO:6, amino acids 3673-3745 of SEQ ID NO:6, and amino acids 2093-2164 of SEQ ID NO:7.

86. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is a dehydratase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7.

87. An isolated polypeptide according to claim 86, wherein said dehydratase domain comprises an amino acid sequence selected from the group consisting of: amino acids 869-1037 of SEQ ID NO:4, amino acids 3886-4048 of SEQ ID NO:5, amino acids 5964-6132 of SEQ ID NO:5, amino acids 2383-2551 of SEQ ID NO:6, and amino acids 887-1051 of SEQ ID NO:7.

88. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is a β-ketoreductase domain comprising an amino acid sequence substantially similar to an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7.

89. An isolated polypeptide according to claim 88, wherein said β-ketoreductase domain comprises an amino acid sequence selected from the group consisting of: amino acids 1439-1684 of SEQ ID NO:4, amino acids 1147-1399 of SEQ ID NO:5, amino acids 2645-2895 of SEQ ID NO:5, amino acids 4729-4974 of SEQ ID NO:5, amino acids 6857-7101 of SEQ ID NO:5, amino acids 1143-1393 of SEQ ID NO:6, amino acids 3392-3636 of SEQ ID NO:6, and amino acids 1810-2055 of SEQ ID NO:7.

90. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is a methyltransferase domain comprising an amino acid sequence substantially similar to amino acids 2671-3045 of SEQ ID NO:6.

91. An isolated polypeptide according to claim 90, wherein said methyltransferase domain comprises amino acids 2671-3045 of SEQ ID NO:6.

92. An isolated polypeptide according to claim 77, wherein said epothilone synthase domain is a thioesterase domain comprising an amino acid sequence substantially similar to amino acids 2165-2439 of SEQ ID NO:7.

93. An isolated polypeptide according to claim 77, wherein said thioesterase domain comprises amino acids 2165-2439 of SEQ ID NO:7.

SEQUENCE LISTING

<110> Novartis AG

<120> GENES FOR THE BIOSYNTHESIS OF EPOTHILONES

<130> 4-30582A

<140>
<141>

<160> 30

<170> PatentIn Ver. 2.0

<210> 1
<211> 68750
<212> DNA
<213> Sorangium cellulosum

<400> 1
aagcttcgct cgacgccctc ttcgcccgcg ccacctctgc ccgtgtgctc gatgatggcc 60
acggccgggc cacggagcgg catgtgctcg ccgaggcgcg cgggatcgag gacctccgcg 120
ccctccgaga gcacctccgc atccaggaag gggggccgtc ctttcactgc atgtgcctcg 180
gcgacctgac ggtggagctc ctcgcgcacg accagcccct cgcgtccatc agcttccacc 240
atgcccgcag cctgaggcac cccgactgga cctcggacgc gatgctcgtc gacggccccg 300
cgctcgtccg gtggctcgcc gcgcgcggcg cgccgggtcc cctccgcgag tacgaagagg 360
agcgcgagcg agcccgaacc gcgcaggagg cgaggcgcct gtggctcgcg gccgcgccgc 420
cctgcttcgc gcccgatctg ccccgcttcg aggacgacgc caacgggctg ccgctcggcc 480
cgatgtcgcc tgaagtcgcc gaggccgagc ggcgcctccg cgcctcgtac gcgactcctg 540
agctcgcctg tgccgcgctg ctcgcctggc tcgggacggg cgcgggtccc tggtccggat 600
atcccgccta cgagatgctg ccagagaatc tgctcctcgg gtttggcctc ccgaccgcga 660
tcgccgcggc ctccgcgccc ggcacatcgg aggccgctct ccgcggcgca gcgcggctgt 720
tcgcctcctg ggaggtcgta tcgagcaaga agagccagct cggcaacatc cccgaagccc 780
tgtgggagcg gctccggacg atcgtccgcg cgatgggcaa tgccgacaac ctctctcgct 840
tcgagcgcgc cgaggcgatc gcggcggagg tgcgccgcct gcgcgcacag ccggcgccct 900
tcgcggcggg cgccggcctg gcggtcgctg ggtctcctc gagcggccgg ctctcgggcc 960
tcgtgaccga cggagacgca ttgtactccg gcgacggcaa cgacatcgtc atgttccaac 1020
ccggccggat ctcgccggtc gtgctgctcg ccggaaccga tcccttcttc gagctcgcac 1080
cgcccctcag ccagatgctc ttcgtcgcgc acgccaacgc gggcaccatc tccaaggtcc 1140
tgacggaagg cagcccccctc atcgtgatgg caagaaacca ggcgcgaccg atgagcctcg 1200
tccacgctcg cgggttcatg gcgtgggtca accaggccat ggtgcccgac cccgagcggg 1260
gcgcgccctt cgtcgtccag cgctcgacca tcatggaatt cgagcacccc acgcctcgtt 1320
gtctccacga gcccgccggc agcgctttct ccctcgcctg cgacgaggag cacctctact 1380
ggtgcgagct ttcggctggc cggctcgagc tatggcgcca cccgcaccac cgcccggcg 1440
ccccgagccg ctttcgcgtac ctcggcgagc accccattgc ggcgacctgg taccccctcgc 1500
tcaccctcaa tgcgacccac gtgctgtggg ccgaccctga tcgcagggcc atcctcgggg 1560
tcgacaagcg caccggcgta gagcccatcg tcctcgcgga gacgcgccat cccccggcgc 1620
acgtcgtgtc cgaggaccgg gacatcttcg cgcttaccgg acagcccgac tcccgcgact 1680
ggcacgtcga gcacatccgc tccggcgcct ccaccgtcgt ggccgactac cagcgccagc 1740
tatgggaccg ccctgacatg gtgctcaatc ggcgcggcct cttcttcacg acgaacgacc 1800
gcatcctgac gctcgcccgc agctgacatc gctcgacgcc gggccgctca tcgagggcgc 1860
ccggaccgag ctggcgaccc gccgctggcg ggccgcagct catgccgatt cggtggcgac 1920
gtagacgctg cgccagaaac gctcgagagc cccgagaac aggaagccgg cggattgtgt 1980
catcacgatc ccgatcagct cgcggcccgg atcattgatc caggacgtcc cgaacccgcc 2040
gtcccaccca tagcgcccgg gcacctccga gaccgcgtcc ggcgccgtga ccacggccat 2100
cccataaccc cagccgtgcg tctcgaagaa gcccgggaaa aacgaggacg ccgccttctg 2160
ggccggcgtg aggtgatcgg ccgtcatctc gcgcaccgag gcggcgctca agagccgccg 2220
gccctcgtgc acaccgccgt tcatgagcat gcgcgcgaac aggaggtagt cgtccaccgt 2280
cgacacgagc ccggcggcgc ccgaagggaa cgccggcggg ctggcatagg cgctctcggc 2340
cccgtcgcga tccatgcgcg tcttctcccc cgtctgctcg tcggtgaagt aaccgcagcc 2400
cgcgaaccga gcgagcttgt ccgccgggac gtgaaagtcg gtgtcccgca tcccgagcgg 2460
cgcgaggatg cgctcgcgca cgaacgcatc gaagccctgg tcggccgcgc gccccacgag 2520
cacccccctgc accaggctcc ccgtgttgta catccactgc gcccccggct gatgcatgag 2580
cggcagcgtc ccgagccgcc ggatccactc gtctggcccg tgcggcgtca tcggcaccgg 2640

ctgcgcgttg acgagcccga gctcgtcgat ggcccgctgg atcggcgacg atgcgtcgaa 2700
cgagattccg aagcccatcg tgaacgtcat caggtcgcgc accgtgatcg gccgctccgc 2760
gggcaccgtc tcgtcgatcg gaccatcgat gcgcgccagc accttccggt tcgcgagctc 2820
cggcaaccat cggtcgacgg gggagtcgag gtcgagcttg ccttcctcga cgagcatcat 2880
caccgccgtc gcggtgaccg ccttcgtcat cgaggcgatc cggaagatcg tgtcccgccg 2940
catgggcgcg ctgccgccga gctcggtcac gcccaccgcg tccacgtgca cgtcgtcgcc 3000
gcgcgcgacc agccagaccg ctcccggcat ctgccccgcc gccacctccg ccgccatcac 3060
ctcgcgcgcg ggcgccagcg cgccggcccc cgcgtcctgc cctggctgcc cctcctcctc 3120
ggccccaccc aacgcgcacc ccggcgccgc cacgctgatc aaagctccca taaactcccg 3180
ccttctcatg accgtcgatg cctctccgag cgggggcgcc tgcccctgcc gagagcactg 3240
actgcccgcg cccgaaaaaa tcatcggtgc cccgtcacga tcgccgccgg gcgtggctcc 3300
gcccggccgc ccgctcgggc gcccgcccct ggacgagcaa agctcgcccg cccgcgctca 3360
gcacgccgct tgccatgtcc ggcctgcacc cacaccgagg agccacccac cctgatgcac 3420
ggcctcaccg agcggcaggt cctgctctcg ctcgtcaccc tcgcgctcat cctcgtgacc 3480
gcgcgcgcct ccggcgagct cgcgcggcgg ctgcgccagc ccgaggtgct cggggagctc 3540
ttcggcggcg tcgtgctggg cccctccgtc gtcggcgcgc tcgcgcccgg gttccatcga 3600
gccctcttcc aggagccggc ggtcggggtc gtgctctcgg gcatctcctg gataggcgcg 3660
ctcctcctgc tgctgatggc gggcatcgag gtcgacgtgg gcatcctgcg caaggaggcg 3720
cgccccgggg cgctctcggc gctcggcgcg atcgcgcccc cgctcgcggc gggcgccgcc 3780
ttctcggcgc tcgtgctcga tcggcccctt ccgagcggcc tcttcctcgg gatcgtgctc 3840
tcggtgacgg cggtcagcgt gatcgcgaag gtgctgatcg agcgcgagtc gatgcgccgc 3900
agctatgcgc aggtgacgct cgcggcgggg gtggtcagcg aggtcgctgc ctgggtgctc 3960
gtcgcgatga cgtcgtcgag ctacggcgcg tcgcccgcgc tggcggtcgc ccggagcgcg 4020
ctcctggcga gcggattctt gctgttcatg gtgctcgtcg ggcggcggct cacccacctc 4080
gcgatgcgct gggtggccga cgcgacgcgc gtctccaagg gacaggtgtc gctcgtcctc 4140
gtcctcacgt tcctggccgc ggcgctgacg cagcggctcg gcctgcaccc gctgctcggc 4200
gcgttcgcgc tcggcgtgct gctcaacagc gctcctcgca ccaaccgccc tctcctcgac 4260
ggcgtgcaga cgctcgtggc gggcctcttc gcgcctgtgt tcttcgtcct cgcgggcatg 4320
cgcgtcgacg tgtcgcagct gcgcacgccg gcggcgtggg ggacggtcgc gttgctgctg 4380
gcgaccgcga cggcggcgaa ggtcgtcccc gccgcgctcg gcgcgcggct cggcgggctc 4440
aggggcagcg aggcggcgct cgtggcggtg ggcctgaaca tgaagggcgg cacggacctc 4500
atcgtcgcga tcgtcggcgt cgagctcggg ctcctctcca acgaggctta tacgatgtac 4560
gccgtcgtcg cgctggtcac ggtgaccgcc tcacccgcgc tcctcatctg gctcgagaaa 4620
agggcgcctc cgacgcagga ggagtcggct cgcctcgagc gcgaggaggc cgcgaggcgc 4680
gcgtacatcc ccggggtcga gcggatcctc gtcccgatcg tggcgcacgc cctgcccggg 4740
ttcgccacgg acatcgtgga gagcatcgtc gcctccaagc gaaagctcgg cgagacggtc 4800
gacatcacgg agctctccgt ggagcagcag gcgcccggcc catcgcgcgc cgcgggggag 4860
gcgagccggg ggctcgcgag gctcggcgcg cgcctccgcg tcggcatctg gcggcaaagg 4920
cgcgagctgc gcggctcgat ccaggcgatc ctgcgcgcct cgcgggatca cgatctgctc 4980
gtgatcggcg cgcgatcgcc ggcgcgcgcg cgcggaatgt cgttcggtcg cctgcaggac 5040
gcgatcgtcc agcgggccga gtccaacgtg ctcgtcgtgg tgggcgaccc tccggcggcg 5100
gagcgcgcct ccgcgcggcg gatcctcgtc ccgatcatcg gcctcgagta ctccttcgcc 5160
gccgccgatc tcgcggccca cgtggcgctg gcgtgggacg ccgagctcgt gctgctcagc 5220
agcgcgcaga ccgatccggg cgcggtcgtc tggcgcgatc gcgagccatc ccgggtgcgc 5280
gcggtggcgc ggagcgtcgt cgacgaggcg gtcttccggg ggcgccggct cggcgtgcgc 5340
gtctcgtcgc gcgtgcacgt gggcgcgcac ccgagcgacg agataacgcg ggagctcgcg 5400
cgcgccccgt acgatctgct cgtgctcgga tgctacgacc atgggccgct cggccggctc 5460
tacctcggca gcacggtcga gtcggtggtg gtccggagcc gggtgccggt cgcgttgctc 5520
gtcgcgcatg gagggactcg agagcaggtg aggtgaggct tccaccgcgc tcgcccgtga 5580
ggaagcgagc gcccggctct gccgacgatc gtcactcccg gtccgtgtag gcgatcgtgc 5640
tgagcagcgc gttctccgcc tgacgcgagt cgagccgggt atgctgcacg acgatggggg 5700
cgtccgattc gatcacgctg gcatagtccg tatcgcgcgg gatcggctcg ggttcggtca 5760
gatcgttgaa ccggacgtgc cgggtgcgcc tcgctggaac ggtcacccgg taaggcccgg 5820
cggggtcgcg gtcgctgaag taaacggtga tggcgacctg cgcgtcccgg tccgacgcat 5880
tcaacaggca ggccgtctca tggctcgtca tctgcggctc aggtccgttg ctcccgcctg 5940
ggatgtagcc ctctgcgatt gcacagcgcg tccgcccgat cggcttgtcc atgtgtcctc 6000
cctcctggct cctctttggc agcctccctc tgctgtccag gagcgatggc ctcttcgctc 6060
gacgcgctcg gggatccatg gctgaggatc ctcgccgagc gctccctgcc gaccggcgcg 6120
ccgagcgccg acgggctttg aaagcgcgcg accggccagc ccggacgcgg gcccgagagg 6180
gacagtgggt ccgccgtgaa gcagagaggc gatcgaggtg gtgagatgaa acacgtcgac 6240
acgggccgac gattcggccg ccggataggg cacacgctcg gtcttctcgc gagcatggcg 6300
ctcgccggct gcggcggtcc gagcgagaaa accgtgcagg gcacgcggct cgcgcccggc 6360
gccgatgcgc gcgtcaccgc cgacgtcgac cccgacgccg cgaccacgcg gctggcggtg 6420
gacgtcgttc acctctcgcc gcccgagcgg ctcgaggccg gcagcgagcg gttcgtcgtc 6480
tggcagcgtc cgagccccga gtccccgtgg cgacgggtcg gagtgctcga ctacaatgct 6540

gacagccgaa gaggcaagct ggccgagacg accgtgccgt atgccaactt cgagctgctc 6600
atcaccgccg agaagcagag cagccctcag tcgccatcgt ctgccgccgt catcgggccg 6660
acgtctgtcg ggtgacatcg cgctatcagc agcgctgagc ccgccagcag gccccagggc 6720
cctgcctcga tggccttccc catcacccct gcgcactcct ccagcgacgg ccgcgcagcg 6780
acggccgcgt ccaagcaacc gccgtgccgg cgcggctcca cgcgcgcgac aggcgagcgt 6840
cctggcgcgg cctgcgcatc gctggaagga tcggcggagc atggatagag aatcgaggat 6900
cgcgatcttt gttgccatcg cagccaacgt ggcgatcgcg gcggtcaagt tcatcgccgc 6960
cgccgtgacc ggcagctcgg cgaggcgttt gccgacttcg gcggcgtccc gcgcgtgctg 7020
ctctacgaca acctcaagag cgccgtcgtc gagcgccacg gcgacgcgat ccggttccac 7080
cccacgctgc tggctctgtc ggcgcattac cgcttcgagc cgcgccccgt cgccgtcgcc 7140
cgcggcaacg agaagggccg cgtccagcgc gccatcacgg cgtggacgac atggcgcgga 7200
aacgtcgtcg taaccgccca gcaatgtcat gggaatggcc ccttgaaatg gccccttgag 7260
ggggctggcc ggggtcgacg atatcgcgcg atctccccgt caattcccga tggtaaaaga 7320
aaaatttgtc atagatcgta agctgtgata gtggtctgtc ttacgttgcg tcttccgcac 7380
ctcgagcgag ttctctcgga taactttcaa tttttccgag gggggcttgg tctctggttc 7440
ctcaggaagc ctgatcggga cgagctaatt cccatccatt tttttgaggc tctgctcaaa 7500
gggattagat cgagtgagac agttcttttg cagtgcgcga agaacctggg cctcgaccgg 7560
aggacgatcg acgtccgcga gcgggtcagc cgctgaggat gtgcccgtcg tggcggatcg 7620
tcccatcgag cgcgcagccg aagatccgat tgcgatcgtc ggagcgagtt gccgtctgcc 7680
cggtggcgtg atcgatctga gcgggttctg gacgctcctc gagggctcgc gcgacaccgt 7740
cgggcgagtc cccgccgaac gctgggatgc agcagcgtgg tttgatcccg accccgatgc 7800
cccggggaag acgcccgtta cgcgcgcatc tttcctgagc gacgtagcct gcttcgacgc 7860
ctccttcttc ggcatctcgc ctcgcgaagc gctgcggatg gaccctgcac atcgactctt 7920
gctggaggtg tgctgggagg cgctggagaa cgccgcgatc gctccatcgg cgctcgtcgg 7980
tacggaaacg ggagtgttca tcgggatcgg cccgtccgaa tatgaggccg cgctgccgca 8040
agcgacggcg tccgcagaga tcgacgctca tggcgggctg gggacgatgc ccagcgtcgg 8100
agcgggccga atctcgtatg ccctcgggct gcgagggccg tgtgtcgcgg tggatacggc 8160
ctattcgtcc tcgctggtgg ccgttcatct ggcctgtcag agcttgcgct ccggggaatg 8220
ctccacggcc ctggctggtg gggtatcgct gatgttgtcg ccgagcaccc tcgtgtggct 8280
ctcgaagacc cgggcgctgg ccagggacgg tcgctgcaag gcattttcgg cggaggccga 8340
tgggttcgga cgaggcgaag ggtgcgccgt cgtggtcctc aagcggctca gtggagcccg 8400
cgcggacggc gatcggatat tggcggtgat tcgaggatcc gcgatcaatc acgacggtgc 8460
gagcagcggt ctgaccgtgc cgaacgggag ctcccaagaa atcgtgctga aacgggccct 8520
ggcggacgca ggctgcgccg cgtcttcggt gggttatgtc gaggcacacg gcacgggcac 8580
gacgcttggt gaccccatcg aaatccaagc tctgaatgcg gtatacggcc tcgggcgaga 8640
tgtcgccacg ccgctgctga tcgggtcggt gaagaccaac cttggccatc ctgagtatgc 8700
gtcggggatc actgggctgc tgaaggtcgt cttgtccctt cagcacgggc agattcctgc 8760
gcacctccac gcgcaggcgc tgaacccccg gatctcatgg ggtgatcttc ggctgaccgt 8820
cacgcgcgcc cggacaccgt ggccggactg gaatacgccg cgacgggcgg gggtgagctc 8880
gttcggcatg agcgggacca acgcgcacgt ggtgctggaa gaggcgccgg cggcgacgtg 8940
cacaccgccg gcgccggagc gaccggcaga gctgctggtg ctgtcggcaa ggaccgcgtc 9000
agccctggat gcacaggcgg cgcggctgcg cgaccatctg gagacctacc cttcgcagtg 9060
tctgggcgat gtggcgttca gtctggcgac gacgcgcagc gcgatggagc accggctcgc 9120
ggtggcggcg acgtcgaggg aggggctgcg ggcagccctg gacgctgcgg cgcagggaca 9180
gacgtcgccc ggtgcggtgc gcagtatcgc cgattcctca cgcggcaagc tcgccttttct 9240
cttcaccgga cagggggcgc agacgctggg catgggccgt gggctgtacg atgtatggtc 9300
cgcgttccgc gaggcgttcg acctgtgcgt gaggctgttc aaccaggagc tcgaccggcc 9360
gctccgcgag gtgatgtggg ccgaaccggc cagcgtcgac gccgcgctgc tcgaccagac 9420
agccttcacc cagccggcgc tgttcacctt cgaatatgcg ctcgccgcgc tgtggcggtc 9480
gtggggtgta gagccggagt tggtcgccgg ccatagcatc ggtgagctgg tggctgcctg 9540
cgtggcgggc gtgttctcgc ttgaggacgc ggtgttcctg gtggctgcgc gcgggcgcct 9600
gatgcaggcg ctgccggccg gcggggcgat ggtgtcgatc gaggcgccgg aggccgatgt 9660
ggctgctgcg gtggcgccgc acgcagcgtc ggtgtcgatc gccgcggtca acgctccgga 9720
ccaggtggtc atcgcgggcg ccgggcaacc cgtgcatgcg atcgcggcgg cgatggccgc 9780
gcgcggggcg cgaaccaagg cgctccacgt ctcgcatgcg ttccactcac cgctcatggc 9840
cccgatgctg gaggcgttcg ggcgtgtggc cgagtcggtg agctaccggc ggccgtcgat 9900
cgtcctggtc agcaatctga gcgggaaggc ttgcacagac gaggtgagct cgccgggcta 9960
ttgggtgcgc cacgcgcgag aggtggtgcg cttcgcggat ggagtgaagg cgctgcacgc 10020
ggccggtgcg ggcaccttcg tcgaggtcgg tccgaaatcg acgctgctcg gcctggtgcc 10080
tgcctgcatg ccggacgccc ggccggcgct gctcgcatcg tcgcgcgctg ggcgtgacga 10140
gccggcgacc gtgctcgagg cgctcggcgg gctctgggcc gtcggtggcc tggtctcctg 10200
ggccggcctc ttcccctcag gggggcggcg ggtgccgctg cccacgtacc cttggcagcg 10260
cgagcgctac tggatcgaca cgaaagccga cgacgcggcg cgtggcgacc gccgtgctcc 10320
gggagcgggt cacgacgagg tcgaggaggg gggcgcggtg cgcggcggcg accggcgcag 10380
cgctcggctc gaccatccgc cgcccgagag cggacgccgg gagaaggtcg aggccgccgg 10440

cgaccgtccg ttccggctcg agatcgatga gccaggcgtg cttgatcacc tcgtgcttcg 10500
ggtcacggag cggcgcgccc ctggtctggg cgaggtcgag atcgccgtcg acgcggcggg 10560
gctcagcttc aatgatgtcc agctcgcgct gggcatggtg cccgacgacc tgccgggaaa 10620
gcccaacccct ccgctgctgc tcggaggcga gtgcgccggg cgcatcgtcg ccgtgggcga 10680
gggcgtgaac ggcctcgtgg tgggccaacc ggtcatcgcc ctttcggcgg gagcgtttgc 10740
tacccacgtc accacgtcgg ctgcgctggt gctgcctcgg cctcaggcgc tctcggcgat 10800
cgaggcggcc gccatgcccg tcgcgtacct gacggcatgg tacgcgctcg acagaatagc 10860
ccgccttcag ccgggggagc gggtgctgat ccatgcggcg accggcgggg tcggtctcgc 10920
cgcggtgcag tgggcgcagc acgtgggagc cgaggtccat gcgacggccg gcacgcccga 10980
gaaacgcgcc tacctggagt cgctgggcgt gcggtatgtg agcgattccc gctcggaccg 11040
gttcgtcgcc gacgtgcgcg cgtggacggg cggcgaggga gtagacgtcg tgctcaactc 11100
gctctcgggc gagctgatcg acaagagttt caatctcctg cgatcgcacg gccggtttgt 11160
ggagctcggc aagcgcgact gttacgcgga taaccagctc gggctgcggc cgttcctgcg 11220
caatctctcc ttctcgctgg tggatctccg gggatgatg ctcgagcggc cggcgcgggt 11280
ccgtgcgctc ttggaggagc tcctcggcct gatcgcggca ggcgtgttca cccctccccc 11340
catcgcgacg ctcccgatcg cccgtgtcgc cgatgcgttc cggagcatgg cgcaggcgca 11400
gcatcttggg aagctcgtac tcacgctggg tgacccggag gtccagatcc gtattccaac 11460
ccacgcaggc gccggcccgt ccaccgggga tcgggacctg ctcgacaggc tcgcgtcagc 11520
tgcgccggcc gcgcgcgcgg cggcgctgga ggcgttcctc cgtacgcagg tctcgcaggt 11580
gctgcgcacg cccgaaatca aggtcggcgc ggaggcgctg ttcacccgcc tcggcatgga 11640
ctcgctcatg gccgtggagc tgcgcaatcg tatcgaggcg agcctcaagc tgaagctgtc 11700
gacgacgttc ctgtccacgt cccccaatat cgccttgttg gcccaaaacc tgttggatgc 11760
tctcgccaca gctctctcct tggagcgggt ggcggcggag aacctacggg caggcgtgca 11820
aaacgacttc gtctcatcgg gcgcagatca agactgggaa atcattgccc tatgacgatc 11880
aatcagcttc tgaacgagct cgagcaccag ggtatcaagc tggcggccga tggggagcgc 11940
ctccagatac aggcccccaa gaacgccctg aacccgaacc tgctcgctcg aatctccgag 12000
cacaaaagca cgatcctgac gatgctccgt cagagactcc ccgcagaatc catcgtgccc 12060
gccccagccg agcggcacgc tccgtttcct ctcacagaca tccaagaatc ctactggctg 12120
ggccggacag gagcgtttac ggtccccagc gggatccacg cctatcgcga atacgactgt 12180
acggatctcg acgtgccgag gctgagccgc gcctttcgga aagtcgtcgc gcggcacgac 12240
atgcttcggg cccacacgct gcccgacatg atgcaggtga tcgagcctaa agtcgacgcc 12300
gacatcgaga tcatcgatct gcgcgggctc gaccggagca cacgggaagc gaggctcgtg 12360
tcgttgcgag atgcgatgtc gcaccgcatc tatgacaccg agcgccctcc gctctatcac 12420
gtcgtcgccg ttcggctgga cgagcggcaa acccgtctcg tgctcagtat cgatctcatt 12480
aacgttgacc taggcagcct gtccatcatc ttcaaggact ggctcagctt ctacgaagat 12540
cccgagacct ctctccctgt cctggagctc tcgtaccgcg attatgtact cgcgctggag 12600
tctcgcaaga agtctgaggc gcatcaacga tcgatggatt actggaagcg gcgcatcgcc 12660
gagctcccac ctccgccgac gcttccgatg aaggccgatc catctacccct gaaggagatc 12720
cgcttccggc acacggagca atggctgccg tcggactcct ggggtcgatt gaagcggcgt 12780
gtcggggagc gcgggctgac cccgacgggc gtcatcctgg ctgcattttc cgaggtgatc 12840
gggcgctgga gcgcgagccc ccggtttacg ctcaacataa cgctcttcaa ccggctcccc 12900
gtccatccgc gcgtgaacga tatcaccggg gacttcacgt cgatggtcct cctggacatc 12960
gacaccactc gcgacaagag cttcgaacag cgcgctaagc gtattcaaga gcagctgtgg 13020
gaagcgatgg atcactgcga cgtaagcggt atcgaggtcc agcgagaggc cgcccgggtc 13080
ctggggatcc aacgaggcgc attgttcccc gtggtgctca cgagcgcgct taaccagcaa 13140
gtcgttggtg tcacctcgtt gcagaggctc ggaactccgg tgtacaccag cacgcagact 13200
cctcagctgc tgctggatca tcagctctac gagcacgatg gggacctcgt cctcgcgtgg 13260
gacatcgtcg acggagtgtt cccgcccgac cttctggacg acatgctcga agcgtacgtc 13320
gtttttctcc ggcggctcac tgaggaacca tggggtgaac aggtgcgctg ttcgcttccg 13380
cctgcccagc tagaagcgcg ggcgagcgca aacgcgacca acgcgctgct gagcgagcat 13440
acgctgcacg gcctgttcgc ggcgcgggtc gagcagctgc ccatgcagct cgccgtggtg 13500
tcggcgcgca agacgctcac gtacgaagag ctttcgcgcc gttcgcggcg acttggcgcg 13560
cggctgcgcg agcagggggc acgcccgaac acattggtcg cggtggtgat ggagaaaggc 13620
tgggagcagg ttgtcgcggt tctcgcggtg ctcgagtcag gcgcggccta cgtgccgatc 13680
gatgccgacc taccggcgga gcgtatccac tacctcctcg atcatggtga ggtaaagctc 13740
gtgctgacgc agccatggct ggatggcaaa ctgtcatggc cgccggggat ccagcggctg 13800
ctcgtgagcg aggccggcgt cgaaggcgac ggcgaccagc ctccgatgat gcccattcag 13860
acaccttcgg atctcgcgta tgtcatctac acctcgggat ccacagggtt gcccaagggg 13920
gtgatgatcg atcatcgggg tgccgtcaac accatcctgg acatcaacga gcgcttcgaa 13980
atagggcccg gagacagggt gctggcgctc tcctcgctga gcttcgatct ctcggtctat 14040
gatgtgttcg ggatcctggc ggcgggcggt acgatcgtgg tgccggacgc gtccaagctg 14100
cgcgatccgg cgcattgggc agagttgatc gaacgagaga aggtgacggt gtggaactcg 14160
gtgccggcgc tgatgcggat gctcgtcgag cattttgagg gtcgccccga ttcgctcgct 14220
aggtctctgc ggctttcgct gctgagcggc gactggatcc cggtgggcct gcctggcgag 14280
ctccaggcca tcaggcccgg cgtgtcggtg atcagcctgg gcggggccac cgaagcgtcg 14340

atctggtcca tcgggtaccc cgtgaggaac gtcgacctat cgtgggcgag catcccctac 14400
ggccgtccgc tgcgcaacca gacgttccac gtgctcgatg aggcgctcga accgcgcccg 14460
gtctgggttc cggggcaact ctacattggc ggggtcgggc tggcactggg ctactggcgc 14520
gatgaagaga agacgcgcaa gagcttcctc gtgcaccccg agaccgggga gcgcctctac 14580
aagaccggcg atctgggccg ctacctgccc gatggaaaca tcgagttcat ggggcgtgag 14640
gacaaccaaa tcaagcttcg cggataccgc gttgagctcg ggaaatcga ggaaacgctc 14700
aagtcgcatc cgaacgtacg cgacgcggtg attgtgcccg tcgggaacga cgcggcgaac 14760
aagctccttc tagcctatgt ggtcccggag ggcacacgga gacgcgctgc cgagcaggac 14820
gcgagcctca agaccgagcg gatcgacgcg agagcacacg ccgccgaagc ggacggcttg 14880
agcgacggcg agagggtgca gttcaagctc gctcgacacg gactccggag ggacctggac 14940
ggaaagcccg tcgtcgatct gaccgggcag gatccgcggg aggcggggct ggacgtctac 15000
gcgcgtcgcc gtagcgtccg aacgttcctt gaggccccga ttccgtttgt tgagtttggt 15060
cgattcctga gctgcttgag cagcgtggag cccgacggcg cgacccttcc caaattccgt 15120
tatccatcgg cgggcagcac gtacccggtg caaacctacg cgtatgtcaa atccggccgc 15180
atcgagggcg tggacgaggg cttctattat taccacccgt tcgagcaccg tttgctgaag 15240
ctctccgatc acgggatcga gcgcggagcg cacgttcggc aaaacttcga cgtgttcgat 15300
gaagcggcgt tcaacctcct gttcgtgggc aggatcgacg ccatcgagtc gctgtatgga 15360
tcgtcgtcgc gagaattttg cctgctggag gccggatata tggcgcagct cctgatggag 15420
caggcgcctt cctgcaacat cggcgtctgt ccggtggggc aattcaattt tgaacaggtt 15480
cggccggttc tcgacctgcg acattcggac gtttacgtgc acggcatgct gggcgggcgg 15540
gtagacccgc ggcagttcca ggtctgtacg ctcggtcagg attcctcacc gaggcgcgcc 15600
acgacgcgcg gcgcccctcc cggccgcgag cagcacttcg ccgatatgct tcgcgacttc 15660
ttgaggacca aactacccga gtacatggtg cctacagtct tcgtggagct cgatgcgttg 15720
ccgctgacgt ccaacggcaa ggtcgatcgt aaggccctgc gcgagcggaa ggatacctcg 15780
tcgccgcggc attcggggca cacggcgcca cgggacgcct tggaggagat cctcgtcgcg 15840
gtcgtacggg aggtgctcgg gctggaggtg gtcgggctcc agcagagctt cgtcgatctt 15900
ggtgcgacat cgattcacat cgttcgcatg aggagcctgt tgcagaagag gctggatagg 15960
gagatcgcca tcaccgagtt gttccagtac ccgaacctcg gctcgctggc gtccggtttg 16020
cgccgagact cgagagatct agatcagcgg ccgaacatgc aggaccgagt ggaggttcgg 16080
cgcaagggca ggagacgtag ctaagagcgc cgaacaaaac caggccgagc gggccgatga 16140
gccgcaagcc cgcctgcgtc accctgggac tcatctgatc tgatcgcggg tacgcgtcgc 16200
gggtgtgcgc gttgagccgt gttgttcgaa cgctgaggaa cggtgagctc atggaagaac 16260
aagagtcctc cgctatcgca gtcatcggca tgtcgggccg ttttccgggg gcgcgggatc 16320
tggacgaatt ctggaggaac cttcgagacg gcacggaggc cgtgcagcgc ttctccgagc 16380
aggagctcgc ggcgtccgga gtcgaccccg cgctggtgct ggacccgagc tacgtccggg 16440
cgggcagcgt gctggaagac gtcgaccggt tcgacgctgc tttcttcggc atcagcccgc 16500
gcgaggcaga gctcatggat ccgcagcacc ggatcttcat ggaatgcgcc tgggaggcgc 16560
tggagaacgc cggatacgac ccgacggctt acgagggctc tatcggcgtg tacgccggcg 16620
ccaacatgag ctcgtacttg acgtcgaacc tccacgagca cccagcgatg atgcggtggc 16680
ccggctggtt tcagacgttg atcggcaacg acaaggatta cctcgcgacc cacgtctcct 16740
acaggctgaa tctgagaggg ccgagcatct ccgttcaaac tgcctgctcc acctcgctcg 16800
tggcggttca cttggcgtgc atgagcctcc tggaccgcga gtgcgacatg gcgctggccg 16860
gcgggattac cgtccggatc cccatcgag ccggctatgt atatgctgag gggggcatct 16920
tctctcccga cggccattgc cgggccttcg acgccaaggc gaacggcacg atcatgggca 16980
acggctgcgg cgttgtcctc ctgaagccgc tggaccgggc gctctccgat ggtgatcccg 17040
tccgcgcggt tatccttggg tctgccacaa acaacgacgg agcgaggaag atcgggttca 17100
ctgcgcccag tgaggtgggc caggcgcaag cgatcatgga ggcgctggcg ctggcagggg 17160
tcgaggcccg gtccatccaa tacatcgaga cccacgggac cggcacgctg ctcggagacg 17220
ccatcgagac ggcggcgctg cggcgggtgt tcggtcgcga cgcttcggcc cggaggtctt 17280
gcgcgatcgg ctccgtgaag accggcatcg gacacctcga atcggcggct ggcatcgccg 17340
gtttgatcaa gacggtcttg gcgctggagc accggcagct gccgcccagc ctgaacttcg 17400
agtctcctaa cccatcgatc gatttcgcga gcagcccgtt ctacgtcaat acctctctta 17460
aggattggaa taccggctcg actccgcggc gggccggcgt cagctcgttc gggatcggcg 17520
gcaccaacgc ccatgtcgtg ctggaggaag cgcccgcggc gaagcttcca gccgcggcgc 17580
cggcgcgctc tgccgagctc ttcgtcgtct cggccaagag cgcagcggcg ctggatgccg 17640
cggcggcacg gctacgagat catctgcagg cgcaccaggg gatttcgttg ggcgacgtcg 17700
ccttcagcct ggcgacgacg cgcagcccca tggagcaccg gctcgcgatg gcggcgccgt 17760
cgcgcgaggc gttgcgagag gggctcgacg cagcggcgcg aggccagacc ccgccgggcg 17820
ccgtgcgtgg ccgctgctcc ccaggcaacg tgccgaaggt ggtcttcgtc tttcccggcc 17880
agggctctca gtgggtcggc atgggccggc agctcctggc tgaggaaccc gtcttccacg 17940
cggcgctttc ggcgtgcgac cgggccatcc aggccgaagc tggttggtcg ctgctcgcgg 18000
agctcgccgc cgacgaaggg tcctcccagc tcgagcgcat cgacgtggtg cagccggtgc 18060
tgttcgccct cgcggtggca tttgcggcgc tgtggcggtc gtggggtgtc gcgcccgacg 18120
tcgtgatcgg ccacagcatg ggcgaggtag ccgccgcgca tgtggccggg gcgctgtcgc 18180
tcgaggatgc ggtggcgatc atctgccggc gcagccggct gctccggcgc atcagcggtc 18240

```
agggcgagat ggcggtgacc gagctgtcgc tggccgaggc cgaggcggcg ctccgaggct 18300
acgaggatcg ggtgagcgtg gccgtgagca acagcccgcg ctcgacggtg ctctcgggcg 18360
agccggcagc gatcggcgag gtgctgtcgt ccctgaacgc gaagggggtg ttctgccgtc 18420
gggtgaaggt ggatgtcgcc agccacagcc cgcaggtcga cccgctgcgc gaggacctct 18480
tggcagccct gggcgggctc cggccgggtg cggctgcggt gccgatgcgc tcgacggtga 18540
cgggcgccat ggtagcgggc ccggagctcg gagcgaatta ctggatgaac aacctcaggc 18600
agccagtgcg cttcgccgag gtagtccagg cgcagctcca aggcggccac ggtctgttcg 18660
tggagatgag cccgcatccg atcctaacga cttcggtcga ggagatgcgg cgcgcggccc 18720
agcgggcggg cgcagcggtg ggctcgctgc ggcgggggca ggacgagcgc ccggcgatgc 18780
tggaggcgct gggcacgctg tgggcgcagg gctaccctgt accctggggg cggctgtttc 18840
ccgcgggggg gcggcgggta ccgctgccga cctatccctg gcagcgcgag cggtactgga 18900
tcgaagcgcc ggccaagagc gccgcgggcg atcgccgcgg cgtgcgtgcg ggcggtcacc 18960
cgctcctcgg tgaaatgcag accctgtcaa cccagacgag cacgcggctg tgggagacga 19020
cgctggatct caagcggctg ccgtggctcg gcgaccaccg ggtgcaggga gcggtcgtgt 19080
ttccgggcgc ggcgtacctg gagatggcga tttcgtcggg ggccgaggct ttgggcgatg 19140
gccctttgca gataactgac gtggtgctcg ccgaggcgct ggccttcgcg ggcgacgcgg 19200
cggtgttggt ccaggtggtg acgacggagc agccgtcggg gcggctgcag ttccagatcg 19260
cgagccgggc gccgggcgct ggccacgcgt ccttccgggt ccacgctcgc ggcgcgttgc 19320
tccgagtgga gcgcaccgag gtcccggctg ggcttacgct ttccgctgtg cgcgcgcggc 19380
tccaggccag catacccgcc gcggccacct acgcggagct gaccgagatg ggctgcagt 19440
acggccctgc cttccagggg attgctgagc tatggcgggg tgaaggcgag gcgctgggac 19500
gggtacgcct gcccgacgcg gccggctcgg cagcggagta tcggttgcat cctgcgctgc 19560
tggacgcgtg cttccagatc gtcggcagcc tcttcgcccg cagtggcgag gcgacgccgt 19620
gggtgcccgt ggagttgggc tcgctgcggc tcttgcagcg gccttcgggg gagctgtggt 19680
gccatgcgcg cgtcgtgaac catgggcacc aaacccccga tcggcagggc gccgactttt 19740
gggtggtcga cagctcgggt gcagtggtcg ccgaagtttg cgggctcgtg gcgcagcggc 19800
ttccgggagg ggtgcgccgg cgcgaagaag acgattggtt cctggagctc gagtgggaac 19860
ccgcagcggt cggcacagcc aaggtcaacg cgggccggtg gctgctcctc ggcggcggcg 19920
gtgggctcgg cgccgcgttg cgcgcgatgc tggaggccgg cggccatgcc gtcgtgcatg 19980
cggcagagaa caacacgagc gctgccggcg tacgcgcgct cctggcaaag gcctttgacg 20040
gccaggctcc gacggcggtg gtgcacctcg gcagcctcga tgggggtggc gagctcgacc 20100
cagggctcgg ggcgcaaggc gcattggacg cgcccccggag cgccgacgtc agtcccgatg 20160
ccctcgatcc ggcgctggta cgtggctgcg acagcgtgct ctggaccgtg caggccctgg 20220
ccggcatggg ctttcgagac gccccgcgat tgtggctttt gacccgcggc gcacaggccg 20280
tcggcgccgg cgacgtctcc gtgacacagg caccgctgct ggggctgggc cgcgtcatcg 20340
ccatggagca cgcggatctg cgctgcgctc gggtcgacct cgatccagcc cggcccgagg 20400
gggagctcgc tgccctgctg gccgagctgc tggccgacga cgccgaagcg gaagtcgcgt 20460
tgcgcggtgg cgagcgatgc gtcgctcgga tcgtccgccg gcagcccgag acccggcccc 20520
gggggaggat cgagagctgc gttccgaccg acgtcaccat ccgcgcggac agcacctacc 20580
ttgtgaccgg cggtctgggt gggctcggtc tgagcgtggc cggatggctg gccgagcgcg 20640
gcgctggtca cctggtgctg gtgggccgct ccggcgcggc gagcgtggag caacgggcag 20700
ccgtcgcggc gctcgaggcc cgcggcgcgc gcgtcaccgt ggcgaaggcg gatgtcgccg 20760
atcgggcgca gctcgagcgg atcctccgcg aggttaccac gtcggggatg ccgctgcggg 20820
gcgtcgtcca tgcggccggc atcttggacg acgggctgct gatgcagcag actcccgcgc 20880
ggtttcgtaa ggtgatggcg cccaaggtcc agggggcctt gcacctgcac gcgttgacgc 20940
gcgaagcgcc gctttccttc ttcgtgctgt acgcttcggg agtagggctc ttgggctcgc 21000
cgggccaggg caactacgcc gcggccaaca cgttcctcga cgctctggcg caccaccgga 21060
gggcgcaggg gctgccagcg ttgagcgtcg actgggcct gttcgcggag gtgggcatgg 21120
cggccgcgca ggaagatcgc ggcgcgcggc tggtctcccg cggaatgcgg agcctcaccc 21180
ccgacgaggg gctgtccgct ctggcacggc tgctcgaaag cggccgcgct caggtggggg 21240
tgatgccggt gaacccgcgg ctgtgggtgg agctctaccc cgcggcggcg tcttcgcgaa 21300
tgttgtcgcg cctggtgacg gcgcatcgcg cgagcgccgg cgggccagcc ggggacgggg 21360
acctgctccg ccgcctcgcc gctgccgagc cgagcgcgcg gagcgcgctc ctggagccgc 21420
tcctccgcgc gcagatctcg caggtgctgc gcctccccga gggcaagatc gaggtggacg 21480
ccccgctcac gagcctgggc atgaactcgc tgatggggct cgagctgcgc aaccgcatcg 21540
aggccatgct gggcatcacc gtaccggcaa cgctgttgtg gacctatccc acggtggcgg 21600
cgctgagcgg gcatctggcg cgggaggcat gcgaagccgc tcctgtggag tcaccgcaca 21660
ccaccgccga ctctgccgtc gagatcgagg agatgtcgca ggacgatctg acgcagttga 21720
tcgcagcaaa attcaaggcg cttacatgac tactcgcggt cctacggcac agcagaatcc 21780
gctgaaacaa gcggccatca tcattcagcg gctggaggag cggctcgctg ggctcgcaca 21840
ggcggagctg gaacggaccg agccgatcgc catcgtcggt atcggctgcc gcttccctgg 21900
cggtgcggac gctccggaag cgttttggga gctgctcgac gcggagcgcg acgcggtcca 21960
gccgctcgac atgcgctggg cgctggtggg tgtcgctccc gtcgaggccg tgccgcactg 22020
ggcggggctg ctcaccgagc cgatagattg cttcgatgct gcgttcttcg gcatctcgcc 22080
tcgggaggcg cgatcgctcg acccgcagca tcgtctgttg ctggaggtcg cttgggaggg 22140
```

gctcgaggac gccggtatcc cgcccccggtc catcgacggg agccgcaccg gtgtgttcgt 22200
cggcgctttc acggcggact acgcgcgcac ggtcgctcgg ctgccgcgcg aggagcgaga 22260
cgcgtacagc gccaccggca acatgctcag catcgccgcc ggacggctgt cgtacacgct 22320
ggggttgcag ggaccttgcc tgaccgtcga cacggcgtgc tcgtcatcgc tggtggcgat 22380
tcacctcgcc tgccgcagcc tgcgcgcagg agagagcgat ctcgcgttgg cgggaggggt 22440
cagcgcgctc ctctcccccg acatgatgga agccgcggcg cgcacgcaag cgctgtcgcc 22500
cgatggtcgt tgccggacct tcgatgcttc ggccaacggg ttcgtccgtg gcgagggctg 22560
tggcctggtc gtcctcaaac ggctctccga cgcgcaacgg gatggcgacc gcatctgggc 22620
gctgatccgg ggctcggcca tcaaccatga tggccggtcg accgggttga ccgcgcccaa 22680
cgtgctggct caggagacgg tcttgcgcga ggcgctgcgg agcgcccacg tcgaagctgg 22740
ggccgtcgat tacgtcgaga cccacggaac agggacctcg ctgggcgatc ccatcgaggt 22800
cgaggcgctg cgggcgacgg tggggccggc gcgctccgac ggcacacgct gcgtgctggg 22860
cgcggtgaag accaacatcg gccatctcga ggccgcggca ggcgtagcgg gcctgatcaa 22920
ggcagcgctt tcgctgacgc acgagcgcat cccgagaaac ctcaacttcc gcacgctcaa 22980
tccgcggatc cggctcgagg gcagcgcgct cgcgttggcg accgagccgg tgccgtggcc 23040
gcgcacggac cgcccgcgct tcgcgggggt gagctcgttc gggatgagcg gaacgaacgc 23100
gcatgtggtg ctggaagagg cgccggcggt ggagctgtgg cctgccgcgc cggagcgctc 23160
ggcggagctt ttggtgctgt cgggcaagag cgagggggcg ctcgatgcgc aggcggcgcg 23220
gctgcgcgag cacctggaca tgcacccgga gctcgggctc ggggacgtgg cgttcagcct 23280
ggcgacgacg cgcagcgcga tgagccaccg gctcgcggtg gcggtgacgt cgcgcgaggg 23340
gctgctggcg gcgctctcgg ccgtggcgca ggggcagacg ccggcggggg cggcgcgctg 23400
catcgcgagc tcctcgcgcg gcaagctggc gttcctgttc accggacagg gcgcgcagac 23460
gccgggcatg ggccgggggc tttgcgcggc gtggccagcg ttccgggagg cgttcgaccg 23520
gtgcgtggcg ctgttcgacc gggagctgga ccgcccgctg cgcgaggtga tgtgggcgga 23580
ggcggggagc gccgagtcgt tgttgctcga ccagacggcg ttcacccagc ccgcgctctt 23640
cgcggtggag tacgcgctga cggcgctgtg gcggtcgtgg ggcgtagagc cggagctcct 23700
ggttgggcat agcatcgggg agctggtggc ggcgtgcgtg gcgggggtgt tctcgctgga 23760
agatggggtg aggctcgtgg cggcgcgcgg gcggctgatg caggggctct cggcgggcgg 23820
cgcgatggtg tcgctcggag cgccggaggc ggaggtggcg gcggcggtgg cgccgcacgc 23880
ggcgtcggtg tcgatcgcgg cggtcaatgg gccggagcag gtggtgatcg cgggcgtgga 23940
gcaagcggtg caggcgatcg cggcggggtt cgcggcgcgc ggcgcgcgca ccaagcggct 24000
gcatgtctcg cacgcgttcc actcgccgct gatggaaccg atgctggagg agttcgggcg 24060
ggtggcggcg tcggtgacgt accggcggcc aagcgtttcg ctggtgagca acctgagcgg 24120
gaaggtggtc acggacgagc tgagcgcgcc ggggtactgg gtgcggcacg tgcgggaggc 24180
ggtgcgcttc gcggacgggg tgaaggcgct gcacgaagcc ggcgcgggga cgttcgtcga 24240
agtgggcccg aagccgacgc tgctcgggct gttgccagcc tgcctgccgg aggcggagcc 24300
gacgctgctg gcgtcgttgc gcgccgggcg cgaggaggct gcgggggtgc tcgaggcgct 24360
gggcaggctg tgggccgccg gcggctcggt cagctggccg ggcgtcttcc ccacggctgg 24420
gcggcgggtg ccgctgccga cctatccgtg gcagcggcag cggtactgga tcgaggcgcc 24480
ggccgaaggg ctcggagcca cggccgccga tgcgctggcg cagtggttct accgggtgga 24540
ctggcccgag atgcctcgct catccgtgga ttcgcggcga gcccggtccg gcgggtggct 24600
ggtgctggcc gaccggggtg gagtcgggga ggcggccgcg gcggcgcttt cgtcgcaggg 24660
atgttcgtgc gccgtgctcc atgcgcccgc cgaggcctcc gcggttgccg agcaggtgac 24720
ccaggccctc ggtggccgca acgactggca gggggtgctg tacctgtggg gtctggacgc 24780
cgtcgtggag gcgggggcat cggccgaaga ggtcgccaaa gtcacccatc ttgccgcggc 24840
gccggtgctc gcgctgattc aggcgctcgg cacggggccg cgctcacccc ggctctggat 24900
cgtgacccga ggggcctgca cggtgggcgg cgagcctgac gctgcccccct gtcaggcggc 24960
gctgtggggt atgggccggg tcgcggcgct agagcatccc ggctcctggg gcgggctcgt 25020
ggacctggat ccggaggaga gcccgacgga ggtcgaggcc ctggtggccg agctgctttc 25080
gccggacgcc gaggatcagc tggcattccg ccaggggcgc cggcgcgcag cgcggcttgt 25140
ggccgcccca ccggagggaa acgcagcgcc ggtgtcgctg tctgcggagg ggagttactt 25200
ggtgacgggt gggctgggcg cccttggcct cctcgttgcg cggtggttgg tggagcgcgg 25260
ggcggggcac cttgtgctga tcagccggca cggattgccc gaccgcgagg aatggggccg 25320
agatcagccg ccagaggtgc gcgcgcgcat tgcggcgatc gaggcgctgg aggcgcaggg 25380
cgcgcgggtc accgtggcgg cggtcgacgt ggccgatgcc gaaggcatgg cggcgctctt 25440
ggcggccgtc gagccgccgc tgcgggggggt agtgcacgcc gcgggtctgc tcgacgacgg 25500
gctgctggcc caccaggacg ctggtcggct cgcccgggtg ttgcgcccca aggtggaggg 25560
ggcatgggtg ctgcacaccc ttacccgcga gcagccgctg gacctcttcg tactgttttc 25620
ctcggcgtcg ggcgtcttcg gctcgatcgg ccagggcagc tacgcggcag gcaatgcctt 25680
tttggacgcg ctggcggacc tccgccgaac gcaggggctc gccgccctga gcatcgcctg 25740
gggcctgtgg gcggaggggg ggatgggctc gcaggcgcag cgccgggaac acgaggcatc 25800
gggaatctgg gcgatgccga cgagtcgggc cctggcggcg atggaatggc tgctcggtac 25860
gcgcgcgacg cagcgcgtgg tcatccagat ggattgggcc catgcgggag cggcgccgcg 25920
cgacgcgagc cgaggccgct tctgggatcg gctggtaact gccacgaaag aggcctcctc 25980
ctcggccgtg ccagctgtgg agcgctggcg caacgcgtct gttgtggaga cccgctcggc 26040

gctctacgag cttgtgcgcg gcgtggtcgc cggggtgatg ggctttaccg accagggcac 26100
gctcgacgtg cgacgaggct tcgccgagca gggcctcgac tccctgatgg ccgtggagat 26160
ccgcaaacgg cttcagggtg agctgggtat gccgctgtcg gcgacgctag cgttcgacca 26220
tccgaccgtg gagcggctgg tggaatactt gctgagccag gcgctggagc tgcaggaccg 26280
caccgacgtg cggagcgttc ggttgccggc gacagaggac ccgatcgcca tcgtgggtgc 26340
cgcctgccgc ttcccgggcg gggtcgagga cctggagtcc tactggcagc tgttgaccga 26400
gggcgtggtg gtcagcaccg aggtgccggc cgaccggtgg aatggggcag acgggcgcgt 26460
ccccggctcg ggagaggcac agagacagac ctacgtgccc aggggtggct ttctgcgcga 26520
ggtggagacg ttcgatgcgg cgttcttcca catctcgcct cgggaggcga tgagcctgga 26580
cccgcaacag cggctgctgc tggaagtgag ctgggaggcg atcgagcgcg cgggccagga 26640
cccgtcggcg ctgcgcgaga gccccacggg cgtgttcgtg ggcgcgggcc ccaacgaata 26700
tgccgagcgg gtgcaggaac tcgccgatga ggcggcgggg ctctacagcg gcaccggcaa 26760
catgctcagc gttgcggcgg gacggctatc atttttcctg ggcctgcacg ggccgaccct 26820
ggctgtggat acggcgtgct cctcgtcgct ggtggcgctg cacctcggct gccagagctt 26880
gcgacggggc gagtgcgacc aagccctggt tggcggggtc aacatgctgc tctcgccgaa 26940
gaccttcgcg ctgctctcac ggatgcacgc actttcgccc ggcgggcggt gcaagacgtt 27000
ctcggccgac gcggacggct acgcgcgggc cgagggctgc gccgtggtgg tgctcaagcg 27060
gctctccgac gcgcagcgcg accgcgaccc catcctggcg gtgatccggg gtacggcgat 27120
caatcatgat ggcccgagca gcgggctgac agtgcccagc ggccctgccc aggaggcgct 27180
gttacgccag gcgctggcgc acgcaggggt ggttccggcc gacgtcgatt tcgtggaatg 27240
ccacgggacc gggacggcgc tgggcgaccc gatcgaggtg cgtgcgctga gcgacgtgta 27300
cgggcaagcc cgccctgcgg accgaccgct gatcctggga gccgccaagg ccaaccttgg 27360
gcacatggag cccgcggcgg gcctggccgg cttgctcaag gcggtgctcg cgctggggca 27420
agagcaaata ccagcccagc cggagctggg cgagctcaac ccgctcttgc cgtgggaggc 27480
gctgccggtg gcggtggccc gcgcagcggt gccgtggccg cgcacggacc gcccgcgctt 27540
cgcgggggtg agctcgttcg ggatgagcgg aacgaacgcg catgtggtgc tggaagaggc 27600
gccggcggtg gagctgtggc ctgccgcgcc ggagcgctcg gcggagcttt tggtgctgtc 27660
gggcaagagc gagggggcgc tcgatgcgca ggcggcgcgg ctgcgcgagc acctggacat 27720
gcacccggag ctcgggctcg ggacgtggc gttcagcctg gcgacgacgc gcagcgcgat 27780
gaaccaccgg ctcgcggtgg cggtgacgtc gcgcgagggg ctgctggcgg cgctttcggc 27840
cgtggcgcag gggcagacgc cgccgggggc ggcgcgctgc atcgcgagct cgtcgcgcgg 27900
caagctggcg ttcctgttca ccggacaggg cgcgcagacg ccgggcatgg gccgggggct 27960
ttgcgcggcg tggccagcgt tccgggaggc gttcgaccgg tgcgtggcgc tgttcgaccg 28020
ggagctggac cgcccgctgc gcgaggtgat gtgggcggag ccggggagcg ccgagtcgtt 28080
gttgctcgac cagacggcgt tcacccagcc cgcgctcttc acggtggagt acgcgctgac 28140
ggcgctgtgg cggtcgtggg gcgtagagcc ggagctggtg gctgggcata gcgccgggga 28200
gctggtggcg gcgtgcgtgg cgggggtgtt ctcgctggaa gatggggtga ggctcgtggc 28260
ggcgcgcggg cggctgatgc aggggctctc ggcgggcggc gcgatggtgt cgctcggagc 28320
gccggaggcg gaggtggcgg cggcggtggc gccgcacgcg gcgtcggtgt cgatcgcggc 28380
ggtcaatggg ccggagcagg tggtgatcgc gggcgtggag caagcggtgc aggcgatcgc 28440
ggcggggttc gcggcgcgcg gcgcgcgcac caagcggctg catgtctcgc acgcgtccca 28500
ctcgccgctg atggaaccga tgctggagga gttcgggcgg gtggcggcgt cggtgacgta 28560
ccggcggcca agcgtttcgc tggtgagcaa cctgagcggg aaggtggtcg cggacgagct 28620
gagcgcgccg gggtactggg tgcggcacgt gcgggaggcg gtgcgcttcg cggacggggt 28680
gaaggcgctg cacgaagccg gtgcgggcac gttcgtcgaa gtgggcccga agccgacgct 28740
gctcgggctg ttgccagcct gcctgccgga ggcggagccg acgctgctgg cgtcgttgcg 28800
cgccgggcgc gaggaggctg cgggggtgct cgaggcgctg ggcaggctgt gggccgccgg 28860
cggctcggtc agctggccgg gcgtcttccc cacggctggg cggcgggtgc cgctgccgac 28920
ctatccgtgg cagcggcagc ggtactggcc cgacatcgag cctgacagcc gtcgccacgc 28980
agccgcggat ccgacccaag gctggttcta tcgcgtggac tggccggaga tacctcgcag 29040
cctccagaaa tcagaggagg cgagccgcgg gagctggctg gtattggcgg ataagggtgg 29100
agtcggcgag gcggtcgctg cagcgctgtc gacacgtgga cttccatgcg tcgtgctcca 29160
tgcgccggca gagacatccg cgaccgccga gctggtgacc gaggctgccg gcggtcgaag 29220
cgattggcag gtagtgctct acctgtgggg tctggacgcc gtcgtcggtg cggaggcgtc 29280
gatcgatgag atcggcgacg cgacccgtcg tgctaccgcg ccggtgctcg gcttggctcg 29340
gtttctgagc accgtgtctt gttcgccccg actctgggtc gtgacccggg gggcatgcat 29400
cgttggcgac gagcctgcga tcgccccttg tcaggcggcg ttatggggca tgggccgggt 29460
ggcggcgctc gagcatcccg gggcctgggg cgggctcgtg gacctggatc cccgagcgag 29520
cccgccccaa gccagcccga tcgacggcga gatgctcgtc accgagctat tgtcgcagga 29580
gaccgaggat cagctcgcct tccgccatgg gcgccggcac gcggcacggc tggtggccgc 29640
cccgccacag gggcaagcgg caccggtgtc gctgtctgcg gaggcgagct acctggtgac 29700
gggaggcctc ggtgggctgg gcctgatcgt ggcccagtgg ctggtggagc tgggagcgcg 29760
gcacttggtg ctgaccagcc ggcgcgggtt gcccgaccgg caggcgtggt gcgagcagca 29820
gccgcctgag atccgcgcgc ggatcgcagc ggtcgaggcg ctggaggcgc ggggtgcacg 29880
ggtgaccgtg gcagcggtgg acgtggccga cgtcgaaccg atgacagcgc tggtttcgtc 29940

ggtcgagccc ccgctgcgag gggtggtgca cgccgctggc gtcagcgtca tgcgtccact 30000
ggcggagacg gacgagaccc tgctcgagtc ggtgctccgt cccaaggtgg ccgggagctg 30060
gctgctgcac cggctgctgc acggccggcc tctcgacctg ttcgtgctgt tctcgtcggg 30120
cgcagcggtg tggggtagcc atagccaggg tgcgtacgcg gcggccaacg ctttcctcga 30180
cgggctcgcg catcttcggc gttcgcaatc gctgcctgcg ttgagcgtcg cgtggggtct 30240
gtgggccgag ggaggcatgg cggacgcgga ggctcatgca cgtctgagcg acatcggggt 30300
tctgcccatg tcgacgtcgg cagcgttgtc ggcgctccag cgcctggtgg agaccggcgc 30360
ggctcagcgc acggtgaccc ggatggactg ggcgcgcttc gcgccggtgt acaccgctcg 30420
agggcgtcgc aacctgcttt cggcgctggt cgcagggcgc gacatcatcg cgccttcccc 30480
tccggcggca gcaacccgga actggcgtgg cctgtccgtt gcggaagccc gcgtggctct 30540
gcacgagatc gtccatgggg ccgtcgctcg ggtgctgggc ttcctcgacc cgagcgcgct 30600
cgatcctggg atggggttca atgagcaggg cctcgactcg ttgatggcgg tggagatccg 30660
caacctcctt caggctgagc tggacgtgcg gctttcgacg acgctggcct ttgatcatcc 30720
gacggtacag cggctggtgg agcatctgct cgtcgatgta ctgaagctgg aggatcgcag 30780
cgacacccag catgttcggt cgttggcgtc agacgagccc atcgccatcg tgggagccgc 30840
ctgccgcttc ccgggcgggg tggaggacct ggagtcctac tggcagctat tggccgaggg 30900
cgtggtggtc agcgccgagg tgccggccga ccggtgggat gcggcggact ggtacgaccc 30960
tgatccggag atcccaggcc ggacttacgt gaccaaaggc gccttcctgc gcgatttgca 31020
gagattggat gcgaccttct tccgcatctc gcctcgcgag gcgatgagcc tcgacccgca 31080
gcagcggttg ctcctggagg taagctggga agcgctcgag agcgcgggta tcgctccgga 31140
tacgctgcga gatagcccca ccggggtgtt cgtgggtgcg gggcccaatg agtactacac 31200
gcagcggctg cgaggcttca ccgacggagc ggcagggttg tacggcggca ccgggaacat 31260
gctcagcgtt acggctggac ggctgtcgtt tttcctgggt ctgcacggcc cgacgctggc 31320
catggatacg gcgtgctcgt catccctggt cgcgctgcac ctcgcctgcc agagcctgcg 31380
actgggcgag tgcgatcaag cgctggttgg cggggtcaac gtgctgctcg cgccggagac 31440
cttcgtgctg ctctcacgga tgcgcgcgct ttcgcccgac gggcggtgca agacgttctc 31500
ggccgacgcg gacggctacg cgcggggcga ggggtgcgcc gtggtggtgc tcaagcggct 31560
gcgcgatgcg cagcgcgccg gcgactccat cctggcgctg atccggggaa gcgcggtgaa 31620
ccacgacggc ccgagcagcg ggctgaccgt acccaacgga cccgcccagc aagcattgct 31680
gcgccaggcg ctttcgcaag caggcgtgtc tccggtcgac gttgatttcg tggagtgtca 31740
cgggacaggg acggcgctgg gcgacccgat cgaggtgcag gcgctgagcg aggtgtatgg 31800
tccagggcgc tccggggacc gaccgctggt gctgggggcc gccaaggcca acgtcgcgca 31860
tctggaggcg gcatctggct tggccagcct gctcaaggcc gtgcttgcgc tgcggcacga 31920
gcagatcccg gcccagccgg agctggggga gctcaacccg cacttgccgt ggaacacgct 31980
gccggtggcg gtgccacgta aggcggtgcc gtgggggcgc ggcgcacgcc cgcgtcgggc 32040
cggcgtgagc gcgttcgggt tgagcggaac caacgtgcat gtcgtgctgg aggaggcacc 32100
ggaggtggag ccggcgcccg cggcgccggc gcgaccggtg gagctggtcg tgctatcggc 32160
caagagcgcg gcggcgctgg acgccgcggc ggcacggctc tcggcgcacc tgtccgcgca 32220
cccggagctg agcctcggcg acgtggcgtt cagcctggcg acgacgcgca gcccgatgga 32280
gcaccggctc gccatcgcga cgacctcgcg cgaggccctg cgaggcgcgc tggacgccgc 32340
ggcgcagcaa aagacgccgc agggcgcggt gcgcggcaag gccgtgtcct cacgcggtaa 32400
gctggctttc ctgttcaccg gacagggcgc gcaaatgccg ggcatggcc gtgggctgta 32460
cgaaacgtgg cctgcgttcc gggaggcgtt cgaccggtgc gtggcgctct tcgatcggga 32520
gatcgaccag cctctgcgcg aggtgatgtg ggctgcgccg ggcctcgctc aggcggcgcg 32580
gctcgatcag accgcgtacg cgcagccggc tctctttgcg ctggagtacg cgctggctgc 32640
cctgtggcgt tcgtggggcg tggagccgca cgtactgctc ggtcatagca tcggcgagct 32700
ggtcgccgcc tgcgtggcgg gcgtgttctc gctcgaagat gcggtgaggt tggtggccgc 32760
gcgcgggcgg ctgatgcagg cgctacccgc cggcggtgcc atggtagcca tcgcagcgtc 32820
cgaggccgag gtggccgcct ccgtggcgcc ccacgccgcc acggtgtcga tcgccgcggt 32880
caacggtcct gacgccgtcg tgatcgccgg cgccgaggta caggtgctcg ccctcggcgc 32940
gacgttcgcg gcgcgtggga tacgcacgaa gaggctcgcc gtctcccatg cgttccactc 33000
gccgctcatg gatccgatgc tggaagactt ccagcgggtc gctgcgacga tcgcgtaccg 33060
cgcgccagac cgcccggtgg tgtcgaatgt caccggccac gtcgcaggcc ccgagatcgc 33120
cacgcccgag tattgggtcc ggcatgtgcg aagcgccgtg cgcttcggcg acggggcaaa 33180
ggcgttgcat gccgcgggtg ccgccacgtt cgtcgaggtt ggcccgaagc cggtcctgct 33240
cgggctgttg ccagcgtgcc tcggggaagc ggacgcggtc ctcgtgccgt cgctacgcgc 33300
ggaccgctcg gaatgcgagg tggtcctcgc ggcgctcggg gcttggtatg cctggggggg 33360
tgcgctcgac tggaagggcg tgttccccga tggcgcgcgc cgcgtggctc tgcccatgta 33420
tccatggcag cgtgagcgcc attggatgga cctcaccccg cgaagcgccg cgcctgcagg 33480
gatcgcaggt cgctggccgc tggctggtgt cgggctctgc atgcccggcg ctgtgttgca 33540
ccacgtgctc tcgatcggac cacgccatca gcccttcctc ggtgatcacc tcgtgtttgg 33600
caaggtggtg gtgcccggcg cctttcatgt cgcggtgatc ctcagcatcg ccgccgagcg 33660
ctggcccgag cgggcgatcg agctgacagg cgtggagttc ctgaaggcca tcgcgatgga 33720
gcccgaccag gaggtcgagc tccacgccgt gctcaccccc gaagccgccg gggatggcta 33780
cctgttcgag ctggcgaccc tggcggcgcc ggagaccgaa cgccgatgga cgacccacgc 33840

ccgcggtcgg gtgcagccga cagacggcgc gcccggcgcg ttgccgcgcc tcgaggtgct 33900
ggaggaccgc gcgatccagc ccctcgactt cgccggattc ctcgacaggt tatcggcggt 33960
gcggatcggc tggggtccgc tttggcgatg gctgcaggac gggcgcgtcg gcgacgaggc 34020
ctcgcttgcc accctcgtgc cgacctatcc gaacgcccac gacgtggcgc ccttgcaccc 34080
gatcctgctg gacaacggct ttgcggtgag cctgctgtca acccggagcg agccggagga 34140
cgacgggacg cccccgctgc cgttcgccgt ggaacgggtg cggtggtggc gggcgccggt 34200
tggaagggtg cggtgtggcg gcgtgccgcg gtcgcaggca ttcggtgtct cgagcttcgt 34260
gctggtcgac gaaactggcg aggtggtcgc cgaggtggag ggatttgttt gccgccgggc 34320
gccgcgagag gtgttcctgc ggcaggagtc gggcgcgtcg actgcagcct tgtaccgcct 34380
cgactggccc gaagcgccct tgcccgatgc gcctgcggaa cggatcgagg agagctgggt 34440
cgtggtggca gcacctggct cggagatggc cgcggcgctc gcaacacggc tcaaccgctg 34500
cgtcctcgcc gaacccaaag gcctcgaggc ggccctcgcg gggtgtctcc ccgcaggtgt 34560
gatctgcctc tgggaggctg gagcccacga ggaagctccg gcggcggcgc agcgtgtggc 34620
gaccgagggc ctctcggtgg tgcaggcgct cagggaccgc gcggtgcgcc tgtggtgggt 34680
gaccatgggc gcagtggccg tcgaggccgg tgagcgggtg caggtcgcca cagcgccggt 34740
atggggcctc ggccggacag tgatgcagga gcgcccggag ctcagctgca ctctggtgga 34800
tttggagccg gaggccgatg cagcgcgctc agctgacgtt ctgttgcggg agctcggtcg 34860
cgctgacgac gagacacagg tggctttccg ttccggaaag cgccgcgtag cgcggctggt 34920
caaagcgacg acccccgaag ggctcctggt ccctgacgca gagtcctatc gactggaggc 34980
tgggcagaag ggcacattgg accagctccg cctcgcgccg gcacagcgcc gggcacctgg 35040
cccgggcgag gtcgagatca aggtaaccgc ctcggggctc aacttccgga ccgtcctcgc 35100
tgtgctggga atgtatccgg gcgacgccgg gccgatgggc ggagattgtg ccggtgtcgc 35160
cacggcggtg ggccaggggg tgcgccacgt cgcggtcggc gatgctgtca tgacgctggg 35220
gacgttgcat cgattcgtca cggtcgacgc gcggctggtg gtccggcagc ctgcagggct 35280
gactcccgcg caggcagcta cggtgccggt cgcgttcctg acggcctggc tcgctctgca 35340
cgacctgggg aatctgcggc gcggcgagcg ggtgctgatc catgctgcgg ccggcggtgt 35400
gggcatggcc gcggtgcaaa tcgcccgatg gatagggggcc gaggtgttcg ccacggcgag 35460
cccgtccaag tgggcagcgg ttcaggccat gggcgtgccg cgcacgcaca tcgccagctc 35520
gcggacgctg gagtttgctg agacgttccg gcaggtcacc ggcggccggg gcgtggacgt 35580
ggtgctcaac gcgctggccg gcgagttcgt ggacgcgagc ctgtccctgc tgtcgacggg 35640
cgggcggttc ctcgagatgg gcaagaccga catacgggat cgagccgcgg tcgcggcggc 35700
gcatcccggt gttcgctatc gggtattcga catcctggag ctcgctccgg atcgaactcg 35760
agagatcctc gagcgcgtgg tcgagggctt tgctgcggga catctgcgcg cattgccggt 35820
gcatgcgttc gcgatcacca aggccgaggc agcgtttcgg ttcatggcgc aagcgcggca 35880
tcagggcaag gtcgtgctgc tgccggcgcc ctccgcagcg cccttggcgc cgacgggcac 35940
cgtactgctg accggtgggc tgggagcgtt ggggctccac gtggcccgct ggctcgccca 36000
gcagggcgtg ccgcacatgg tgctcacagg tcggcggggc ctggatacgc cgggcgctgc 36060
caaagccgtc gcggagatcg aagcgctcgg cgctcgggtg acgatcgcgg cgtcggatgt 36120
cgccgatcgg aatgcgctgg aggctgtgct ccaggccatt ccggcggagt ggccgttaca 36180
gggcgtgatc catgcagccg gagcgctcga tgatggtgtg cttgatgagc agaccaccga 36240
ccgcttctcg cgggtgctgg caccgaaggt gactggcgcc tggaatctgc atgagctcac 36300
ggcgggcaac gatctcgctt tcttcgtgct gttctcctcc atgtcggggc tcttgggctc 36360
ggccgggcag tccaactatg cggcggccaa caccttcctc gacgcgctgg ccgcgcatcg 36420
gcgggccgaa ggcctggcgg cgcagagcct cgcgtggggc ccatggtcgg acggaggcat 36480
ggcagcgggg ctcagcgcgg cgctgcaggc gcggctcgct cggcatggga tgggagctct 36540
gtcgccggct cagggcaccg cgctgctcgg gcaggcgctg gctcggccgg aaacgcagct 36600
cggggcgatg tcgctcgacg tgcgtgcggc aagccaagct tcgggagcgg cagtgccgcc 36660
tgtgtggcgc gcgttggtgc gcgcggaggc gcgccatacg gcggctgggg cgcagggggc 36720
attggccgcg cgtcttgggg cgctgcccga ggcgcgtcgc gccgacgagg tgcgcaaggt 36780
cgtgcaggcc gagatcgcgc gcgtgctttc atggagcgcc gcgagcgccg tgcccgtcga 36840
tcggccgctg tcggacttgg gcctcgactc gctcacggcg gtggagctgc gcaacgtgct 36900
cggccagcgg gtgggtgcga cgctgccggc gacgctggca ttcgatcacc cgacggtcga 36960
cgcgctcacg cgctggctgc tcgataaggt cctggccgtg gccgagccga gcgtatcgtc 37020
cgcaaagtcg tcgccgcagg tcgccctcga cgagcccatt gccatcatcg gcatcggctg 37080
ccgtttccca ggcggcgtgg ccgatccgga gtcgttttgg cggctgctcg aagagggcag 37140
cgatgccgtc gtcgaggtgc cgcatgagcg atgggacatc gacgcgttct atgatccgga 37200
tccggatgtg cgcggcaaga tgacgacacg ctttggcggc ttcctgtccg atatcgaccg 37260
gttcgatccg gccttcttcg gcatctcgcc gcgcgaagcg acgaccatgg atccgcagca 37320
gcggctgctc ctggagacga gctgggaggc gttcgagcgc gccgggattt tgcccgagcg 37380
gctgatgggc agcgataccg gcgtgttcgt ggggctcttc taccaggagt acgctgcgct 37440
cgccggcggc atcgaggcgt tcgatggcta tctaggcacc ggcaccacgg ccagcgtcgc 37500
ctcgggcagg atctcttatg tgctcgggct aaaggggccg agcctgacgg tggacaccgc 37560
gtgctcctcg tcgctggtcg cggtgcacct ggcctgccag gcgctgcggc ggggcgagtg 37620
ttcggtggcg ctggccggcg gcgtggcgct gatgctcacg ccggcgacgt tcgtggagtt 37680
cagccggctg cgaggcctgg ctcccgacgg acggtgcaag agcttctcgg ccgcagccga 37740

cggcgtgggg tggagcgaag gctgcgccat gctcctgctc aaaccgcttc gcgatgcgca 37800
gcgcgatggg gatccgatcc tggcggtgat ccgcggcacc gcggtgaacc aggatgggcg 37860
cagcaacggg ctgacggcgc ccaacgggtc gtcgcagcaa gaggtgatcc gtcgggccct 37920
ggagcaggcg gggctggctc cggcggacgt cagctacgtc gagtgccacg gcaccggcac 37980
gacgttgggc gaccccatcg aagtgcaggc cctgggcgcc gtgctggcac aggggcgacc 38040
ctcggaccgg ccgctcgtga tcgggtcggt gaagtccaat atcggacata cgcaggctgc 38100
ggcgggcgtg gccggtgtca tcaaggtggc gctggcgctc gagcgcgggc ttatcccgag 38160
gagcctgcat ttcgacgcgc ccaatccgca cattccgtgg tcggagctcg ccgtgcaggt 38220
ggccgccaaa cccgtcgaat ggacgagaaa cggcgtgccg cgacgagccg gggtgagctc 38280
gtttggcgtc agcgggacca acgcgcacgt ggtgctggag gaggcgccag cggcggcgtt 38340
cgcgcccgcg gcggcgcgtt cagcggagct tttcgtgctg tcggcgaaga gcgccgcggc 38400
gctggacgcg caggcggcgc ggctttcggc gcacgtcgtt gcgcacccgg agctcggcct 38460
cggcgacctg gcgttcagcc tggcgacgac ccgcagcccg atgacgtacc ggctcgcggt 38520
ggcggcgacc tcgcgcgagg cgctgtctgc cgcgctcgac acagcggcgc aggggcaggc 38580
gccgcccgca gcggctcgcg gccacgcttc cacaggcagc gccccaaagg tggttttcgt 38640
ctttcctggc cagggctccc agtggctggg catgggccaa aagctcctct cggaggagcc 38700
cgtcttccgc gacgcgctct cggcgtgtga ccgagcgatt caggccgaag ccggctggtc 38760
gctgctcgcc gagctcgcgg ccgatgagac cacctcgcag ctcggccgca tcgacgtggt 38820
gcagccggcg ctgttcgcga tcgaggtcgc gctgtcggcg ctgtggcggt cgtggggcgt 38880
cgagccggat gcagtggtag gccacagcat gggcgaagtg gcggccgcgc acgtcgccgg 38940
cgccctgtcg ctcgaggatg ctgtagcgat catctgccgg cgcagcctgc tgctgcggcg 39000
gatcagcggc caaggcgaga tggcggtcgt cgagctttcc ctggccgagg ccgaggcagc 39060
gctcctgggc tacgaagacc ggctcagcgt ggcggtgagc aacagcccgc gctcgacggt 39120
gctggcgggc gagccggcag cgctcgcaga ggtgctggcg atccttgcgg caaagggggt 39180
gttctgccgt cgagtcaagg tggacgtcgc cagccacagc ccacagatcg acccgctgcg 39240
cgacgagcta ttggcagcat tgggcgagct cgagccgcga caagcgaccg tgtcgatgcg 39300
ctcgacggtg acgagcacga tcatggcggg cccggagctc gtggcgagct actgggcgga 39360
caacgttcga cagccggtgc gcttcgccga agcggtgcaa tcgttgatgg aagacggtca 39420
tgggctgttc gtggagatga gcccgcatcc gatcctgacg acatcggtcg aggagatccg 39480
acgggcgacg aagcgggagg gagtcgcggt gggctcgttg cggcgtggac aggacgagcg 39540
cctgtccatg ttggaggcgc tgggagcgct ctgggtacac ggccaggcgg tgggctggga 39600
gcggctgttc tcccgcgggcg gcgcgggcct ccgtcgcgtg ccgctgccga cctatccctg 39660
gcagcgcgag cggtactggg tcgatgcgcc gaccggcggc gcggcgggcg gcagccgctt 39720
tgctcatgcg ggcagtcacc cgctcctggg tgaaatgcag accctgtcga cccagaggag 39780
cacgcgcgtg tgggagacga cgctggatct caaacggctg ccgtggctcg gcgatcaccg 39840
ggtgcagggg gcggtcgtgt tcccgggcgc ggcgtacctg gagatggcgc tttcgtccgg 39900
ggccgaggcc ttgggtgacg gtccgctcca ggtcagcgat gtggtgctcg ccgaggcgct 39960
ggccttcgcg gatgatacgc cggcggcggt gcaggtcatg gcgaccgagg agcgaccagg 40020
ccgcctgcaa ttccacgttg cgagccgggt gccgggccac ggcggtgctg cctttcgaag 40080
ccatgcccgc ggggtgctgc gccagatcga gcgcgccgag gtcccggcga ggctggatct 40140
ggccgcgctt cgtgcccggc ttcaggccag cgcacccgct gcggctacct atgcggcgct 40200
ggccgagatg gggctcgagt acggcccagc gttccagggg cttgtcgagc tgtggcgggg 40260
ggagggcgag gcgctgggac gtgtgcggct ccccgaggcc gccggctccc cagccgcgtg 40320
ccggctccac cccgcgctct tggatgcgtg cttccacgtg agcagcgcct tcgctgaccg 40380
cggcgaggcg acgccatggg tacccgtgga aatcggctcg ctgcggtggt tccagcggcc 40440
gtcgggggag ctgtggtgtc atgcgcggag tgtgagccac ggaaagccaa cacccgaccg 40500
gcggagtacc gacttctggg tggtcgacag cacgggcgcg atcgtcgccg agatctccgg 40560
gctcgtggcg cagcggctcg cgggaggtgt acgccggcgc gaagaagacg actggttcat 40620
ggagccggct tgggaaccga ccgcggtccc cggatccgag gtcatggcgg gccggtggct 40680
gctcatcggc tcgggcggcg ggctcggcgc tgcgctccac tcggcgctga cggaagctgg 40740
ccattccgtc gtccacgcga cagggcgcgg cacgagcgcc gccgggttgc aggcactctt 40800
gacggcgtcc ttcgacggcc aggccccgac gtcggtggtg cacctcggca gcctcgatga 40860
gcgtggcgtg ctcgacgcgg atgccccctt cgacgccgat gcgcttgagg agtcgctggt 40920
gcgcggctgc gacagcgtgc tctggaccgt gcaggccgtg gccggggcgg gcttccgaga 40980
tcctccgcgg ttgtggctcg tgacacgcgg cgctcaggcc atcggcgccg gcgacgtctc 41040
tgtggcgcaa gcgccgctcc tggggctggg ccgcgttatc gccttggagc acgccgagct 41100
gcgctgcgct cggatcgacc tcgatccagc gcggcgcgac ggagaagtcg atgagctgct 41160
tgccgagctg ttggccgacg acgccgagga ggaagtcgcg tttcgcggcg gtgagcggcg 41220
cgtggcccgg ctcgtccgaa ggctgcccga gaccgactgc cgagagaaaa tcgagcccgc 41280
ggaaggccgg ccgttccggc tggagatcga tgggtccggc gtgctcgacg acctggtgct 41340
ccgagccacg gagcggcgcc ctcctggccc gggcgaggtc gagatcgccg tcgaggcggc 41400
ggggctcaac tttctcgacg tgatgagggc catggggatc taccctgggc ccggggacgg 41460
tccggttgcg ctgggcgccg agtgctccgg ccgaattgtc gcgatgggcg aaggtgtcga 41520
gagccttcgt atcggccagg acgtcgtggc cgtcgcgccc ttcagtttcg gcacccacgt 41580
caccatcgac gcccggatgc tcgcacctcg ccccgcggcg ctgacggccg cgcaggcagc 41640

cgcgctgccc gtcgcattca tgacggcctg gtacggtctc gtccatctgg ggaggctccg 41700
ggccggcgag cgcgtgctca tccactcggc gacgggggc accgggctcg ctgctgtgca 41760
gatcgcccgc cacctcggcg cggagatatt tgcgaccgct ggtacaccgg agaagcgggc 41820
gtggctgcgc gagcagggga tcgcgcacgt gatggactcg cggtcgctgg acttcgccga 41880
gcaagtgctg gccgcgacga agggcgaggg ggtcgacgtc gtgttgaact cgctgtctgg 41940
cgccgcgatc gacgcgagcc tttcgaccct cgtgccggac ggccgcttca tcgagctcgg 42000
caagacggac atctatgcag atcgctcgct ggggctcgct cacttcagga agagcctgtc 42060
ctacagcgcc gtcgatcttg cgggcttggc cgtgcgtcgg cccgagcgcg tcgcagcgct 42120
gctggcggag gtggtggacc tgctcgcacg gggagcgctg cagccgcttc cggtagagat 42180
cttccccctc tcgcgggccg cggacgcgtt ccggaaaatg gcgcaagcgc agcatctcgg 42240
gaagctcgtg ctcgcgctgg aggacccgga cgtgcggatc cgcgttccgg gcgaatccgg 42300
cgtcgccatc cgcgcggacg gcgcctacct cgtgaccggc ggtctggggg ggctcggtct 42360
gagcgtggct ggatggctgg ccgagcaggg ggctgggcat ctggtgctgg tgggccgctc 42420
cggcgcggtg agcgcggagc agcagacggc tgtcgccgcg ctcgaggcgc acggcgcgcg 42480
tgtcacggta gcgagggcag acgtcgccga tcgggcgcag atggagcgga tcctccgcga 42540
ggttaccgcg tcggggatgc cgctccgcgg cgtcgttcat gcggccggaa tcctggacga 42600
cgggctgctg atgcagcaaa cccccgcgcg gttccgcgcg gtcatggcgc ccaaggtccg 42660
aggggccttg cacctgcatg cgttgacacg cgaagcgccg ctctccttct tcgtgctgta 42720
cgcttcggga gcagggctct tgggctcgcc gggccagggc aactacgccg cggccaacac 42780
gttcctcgac gcactggcac accaccggag ggcgcagggg ctgccagcat tgagcatcga 42840
ctggggcctg ttcgcggacg tgggtttggc cgccgggcag caaaatcgcg gcgcacggct 42900
ggtcacccgc gggacgcgga gcctcacccc cgacgaaggg ctgtgggcgc tcgagcgcct 42960
gctcgacggc gatcgcaccc aggccggggt catgccgttc gacgtgcggc agtgggtgga 43020
gttctacccg gcggcggcat cttcgcggag gttgtcgcgg ctcatgacgg cacggcgcgt 43080
ggcttccggt cggctcgccg gggatcggga cctgctcgaa cggctcgcca ccgccgaggc 43140
gggcgcgcgg gcagggatgc tgcaggaggt cgtgcgcgcg caggtctcgc aggtgctgcg 43200
cctctccgaa ggcaagctcg acgtggatgc gccgctcacg agcctgggaa tggactcgct 43260
gatggggcta gagctgcgca accgcatcga ggccgtgctc ggcatcacca tgccggcgac 43320
cctgctgtgg acctacccca cggtggcagc gctgagtgcg catctggctt ctcatgtcgt 43380
ctctacgggg gatggggaat ccgcgcgccc gccggataca gggagcgtgg ctccaacgac 43440
ccacgaagtc gcttcgctcg acgaagacgg gttgttcgcg ttgattgatg agtcactcgc 43500
gcgcgcggga aagaggtgat tgcgtgacag accgagaagg ccagctcctg gagcgcttgc 43560
gtgaggttac tctggcccttt cgcaagacgc tgaacgagcg cgataccctg gagctcgaga 43620
agaccgagcc gatcgccatc gtggggatcg gctgccgctt ccccggcgga gcgggcactc 43680
cggaggcgtt ctgggagctg ctcgacgacg ggcgcgacgc gatccggccg ctcgaggagc 43740
gctgggcgct cgtaggtgtc gacccaggcg acgacgtacc gcgctggcg gggctgctca 43800
ccgaggccat cgacggcttc gacgccgcgt tcttcggtat cgcccccccgg gaggcacggt 43860
cgctcgaccc gcagcatcgc ctgctgctgg aggtcgcctg ggaggggttc gaagacgccg 43920
gcatcccgcc caggtccctc gtcgggagcc gcaccggcgt gttcgtcggc gtctgcgcca 43980
cggagtacct ccacgccgcc gtcgcgcacc agccgcgcga agagcgggac gcgtacagca 44040
ccaccggcaa catgctcagc atcgccgccg gacggctatc gtacacgctg ggctgcagg 44100
gaccttgcct gaccgtcgat acggcgtgct cgtcatcgct ggtggccatt cacctcgcct 44160
gccgcagcct gcgcgctcga gagagcgatc tcgcgctggc gggaggggtc aacatgcttc 44220
tctcccccga cacgatgcga gctctggcgc gcacccaggc gctgtcgccc aatggccgtt 44280
gccagacctt cgacgcgtcg gccaacgggt tcgtccgtgg ggagggctgc ggtctgatcg 44340
tgctcaagcg attgagcgac gcgcggcggg atggggaccg gatctgggcg ctgatccgag 44400
gatcggccat caatcaggac ggccggtcga cggggttgac ggcgcccaac gtgctcgccc 44460
agggggcgct cttgcgcgag gcgctgcgga acgccggcgt cgaggccgag gccatcggtt 44520
acatcgagac ccacggggcg gcaacctcgc tgggcgaccc catcgagatc gaagcgctgc 44580
gcgctgtggt ggggccggcg cgagccgacg gagcgcgctg cgtgctgggc gcggtgaaga 44640
ccaacctcgg ccacctggag ggcgctgccg gcgtggcggg cctgatcaag gcgacgcttt 44700
cgctacatca cgagcgcatc ccgaggaacc tcaactttcg tacgctcaat ccgcggatcc 44760
ggatcgaggg gaccgcgctc gcgttggcga ccgaaccggt gccctggccg cggacgggcc 44820
ggacgcgctt cgcgggagtg agctcgttcg ggatgagcgg gaccaacgcg catgtggtgt 44880
tggaggaggc gccggcggtg gagcctgagg ccgcggcccc cgagcgcgca gcggagctgt 44940
tcgtcctgtc ggcgaagagc gcggcggcgc tggatgcgca ggcagcccgg ctgcgggacc 45000
acctggagaa gcacgtcgag cttggcctcg gcgatgtggc gttcagcctg gcgacgacgc 45060
gcagcgcgat ggagcaccgg ctggcggtgg ccgcgagctc gcgcgaggcg ctgcgagggg 45120
cgctttcggc cgcagcgcag ggcacacgc cgccgggagc cgtgcgtggg cgggcctcgg 45180
gcggcagcgc gccgaaggtg gtcttcgtgt ttcccggtca gggctcgcag tgggtgggca 45240
tgggccgaaa gctcatggcc gaagagccgg tcttccgggc ggcgctggag ggttgcgacc 45300
gggccatcga ggcggaagcg ggctggtcgc tgctcgggga gctctccgcc gacgaggccg 45360
cctcgcagct cgggcgcatc gacgtggttc agccggtgct cttcgccatg gaagtagcgc 45420
tttctgcgct gtggcggtcg tggggagtgg agccggaagc ggtggtgggc cacagcatgg 45480
gcgaggttgc ggcggcgcac gtggccggcg cgctgtcgct cgaggacgcg gtggcgatca 45540

tctgccggcg cagccggctg ctgcggcgga tcagcggtca gggggagatg gcgctggtcg 45600
agctgtcgct ggaggaggcc gaggcggcgc tgcgtggcca tgagggtcgg ctgagcgtgg 45660
cggtgagcaa cagcccgcgc tcgaccgtgc tcgccggcga gccggcggcg ctctcggagg 45720
tgctggcggc gctgacggcc aagggggtgt tctggcggca ggtgaaggtg gacgtcgcca 45780
gccatagccc gcaggtcgac ccgctgcgcg aagagctgat cgcggcgctg ggagcgatcc 45840
ggccgcgagc ggctgcggtg ccgatgcgct cgacggtgac gggcggggtg atcgcgggtc 45900
cggagctcgg tgcgagctac tgggcggaca accttcggca gccggtgcgc ttcgctgcgg 45960
cggcgcaagc gctgctggag ggtggccccg cgctgttcat cgagatgagc ccgcacccga 46020
tcctggtgcc gcccctggac gagatccaga cggcggccga gcaaggggc gctgcggtgg 46080
gctcgctgcg gcgagggcag gacgagcgcg cgacgctgct ggaggcgctg ggacgctgt 46140
gggcgtccgg ctatccggtg agctgggctc ggctgttccc cgcgggcggc aggcgggttc 46200
cgctgccgac ctatccctgg cagcacgagc ggtgctggat cgaggtcgag cctgacgccc 46260
gccgcctcgc cgcagccgac cccaccaagg actggttcta ccgaacggac tggcccgagg 46320
tgccccgcgc cgccccgaaa tcggagacag ctcatgggag ctggctgctg ttggccgaca 46380
ggggtggggt cggtgaggcg gtcgctgcag cgctgtcgac gcgcggactt tcctgcaccg 46440
tgcttcatgc gtcggctgac gcctccaccg tcgccgagca ggtatccgaa gctgccagtc 46500
gccgaaacga ctggcaggga gtcctctacc tgtggggcct cgacgccgtc gtcgatgctg 46560
gggcatcggc cgacgaagtc agcgaggcta cccgccgtgc caccgcaccc gtccttgggc 46620
tggttcgatt cctgagcgct gcgccccatc ctcctcgctt ctgggtggtg acccgcgggg 46680
catgcacggt gggcggcgag ccagaggcct ctctttgcca agcggcgttg tggggcctcg 46740
cgcgcgtcgc ggcgctggag caccccgctg cctggggtgg cctcgtggac ctggatcctc 46800
agaagagccc gacggagatc gagcccctgg tggccgagct gctttcgccg gacgccgagg 46860
atcaactggc gttccgcagc ggtcgcaggc acgcagcacg ccttgtagcc gccccgccgg 46920
agggcgacgt cgcaccgata tcgctgtccg cggaggggag ctacctggtg acgggcgggc 46980
tgggtggcct tggtctgctc gtggctcggt ggctggtgga gcggggagct cgacatctgg 47040
tgctcaccag ccggcacggg ctgccagagc gacaggcgtc gggcggagag cagccgccgg 47100
aggcccgcgc gcgcatcgca gcggtcgagg ggctggaagc gcagggcgcg cgggtgaccg 47160
tggcagcggt ggatgtcgcc gaggccgatc ccatgacggc gctgctggcc gccatcgagc 47220
ccccgttgcg cggggtggtg cacgccgccg gcgtcttccc cgtgcgtcac ctggcggaga 47280
cggacgaggc cctgctggag tcggtgctcc gtcccaaggt ggccgggagc tggctgctgc 47340
accggctgct gcgcgaccgg cctctcgacc tgttcgtgct gttctcgtcg ggcgcggcgg 47400
tgtggggtgg caaaggccaa ggcgcatacg ccgcggccaa tgcgttcctc gacgggctcg 47460
cgcaccatcg ccgcgcgcac tcgctgccgg cgttgagcct cgcctggggc ttatgggccg 47520
agggaggcat ggttgatgca aaggctcatg cacgtctgag cgacatcggg gtcctgccca 47580
tggccacggg gccggccttg tcggcgctgg agcgcctggt gaacaccagc gctgtccagc 47640
gttcggtcac acggatggac tgggcgcgct tcgcgccggt ctatgccgcg cgagggcggc 47700
gcaacttgct ttcggctctg gtcgcggagg acgagcgcgc tgcgtctccc ccggtgccga 47760
cggcaaaccg gatctggcgc ggcctgtccg ttgcggagag ccgctcagcc ctctacgagc 47820
tcgttcgcgg catcgtcgcc cgggtgctgg gcttctccga cccgggcgcg ctcgacgtcg 47880
gccgaggctt cgccgagcag gggctcgact ccctgatggc tctggagatc cgtaaccgcc 47940
ttcagcgcga gctgggcgaa cggctgtcgg cgactctggc cttcgaccac ccgacggtgg 48000
agcggctggt ggcgcatctc ctcaccgacg tgctgaagct ggaggaccgg agcgacaccc 48060
ggcacatccg gtcggtggcg gcggatgacg acatcgccat cgtcggtgcc gcctgccggt 48120
tcccaggtgg ggatgagggc ctggagacat actggcggca tctggccgag ggcatggtgg 48180
tcagcaccga ggtgccagcc gaccggtggc gcgcggcgga ctggtacgac cccgatccgg 48240
aggttccggg ccggacctat gtggccaagg gtgccttcct ccgcgatgtg cgcagcttgg 48300
atgcggcgtt cttcgccatt tcccctcgtg aggcgatgag cctggacccg caacagcggc 48360
tgttgctgga ggtgagctgg gaggcgatcg agcgcgctgg ccaggacccg atggcgctgc 48420
gcgagagcgc cacgggcgtg ttcgtgggca tgatcgggag cgagcacgcc gagcgggtgc 48480
agggcctcga cgacgacgcg gcgttgctgt acggcaccac cggcaacctg ctcagcgtcg 48540
ccgctggacg gctgtcgttc ttcctgggtc tgcacggccc gacgatgacg gtggacaccg 48600
cctgctcgtc gtcgctggtg gcgttgcacc tcgcctgcca gagcctgcga ttgggcgagt 48660
gcgaccaggc cctggccggc gggtccagcg tgcttttgtc gccgcggtca ttcgtcgcgg 48720
cgtcgcgcat gcgtttgctt tcgccagatg ggcggtgcaa gacgttctcg gccgctgcag 48780
acggctttgc gcgggccgag ggctgcgccg tggtggtgct caagcggctc cgtgacgcgc 48840
agcgcgaccg cgaccccatc ctggcggtgg tcaggagcac ggcgatcaac cacgatggcc 48900
cgagcagcgg gctcacggtg cccagcggtc ctgcccagca ggcgttgcta cgccaggcgc 48960
tggcgcaagc gggcgtggcg ccggccgagg tcgatttcgt ggagtgccac gggacgggga 49020
cagcgctggg tgacccgatc gaggtgcagg cgctgggcgc ggtgtacggg cggggccgcc 49080
ccgcggagcg gccgctctgg ctgggcgctg tcaaggccaa cctcggccac ctggaggccg 49140
cggcgggctt ggccggcgtg ctcaaggtgc tcttggcgct ggagcacgag cagattccgg 49200
ctcaaccgga gctcgacgag ctcaacccgc acatcccgtg ggcagagctg ccagtggccg 49260
ttgtccgcag ggcggtcccc tggccgcgcg gcgcgcgccc gcgtcgtgca ggcgtgagcg 49320
ctttcggcct gagcgggacc aacgcgcatg tggtgttgga ggaggcgccg gcggtggagc 49380
ctgtggccgc ggcccccgag cgcgcagcgg agctgttcgt cctgtcggcg aagagcgcgg 49440

cggcgctgga tgcgcaggca gcccggctgc gggaccacct ggagaagcat gtcgagcttg 49500
gcctcggcga tgtggcgttc agcctggcga cgacgcgcag cgcgatggag caccggctgg 49560
cggtggccgc gagctcgcgc gaggcgctgc gaggggcgct ttcggccgca gcgcaggggc 49620
acacgccgcc gggagccgtg cgtgggcggg cctcgggcgg cagcgcgccg aaggtggtct 49680
tcgtgtttcc cggccagggc tcgcagtggg tgggcatggg ccgaaagctc atggccgaag 49740
agccggtctt ccgggcggcg ctggagggtt gcgaccgggc catcgaggcg gaagcgggct 49800
ggtcgctgct cggggagctc tccgccgacg aggccgcctc gcagctcggg cgcatcgacg 49860
tggttcagcc ggtgctgttc gccatggaag tagcgctttc tgcgctgtgg cggtcgtggg 49920
gagtggagcc ggaagcggtg gtgggccaca gcatgggcga ggttgcggcg gcgcacgtgg 49980
ccggcgcgct gtcgctcgag gacgcggtgg cgatcatctg ccggcgcagc cggctgctgc 50040
ggcggatcag cggtcagggg gagatggcgc tggtcgagct gtcgctggag gaggccgagg 50100
cggcgctgcg tggccatgag ggtcggctga gcgtggcggt gagcaacagc ccgcgctcga 50160
ccgtgctcgc cggcgagccg gcggcgctct cggaggtgct ggcggcgctg acggccaagg 50220
gggtgttctg gcggcaggtg aaggtggacg tcgccagcca tagcccgcag gtcgacccgc 50280
tgcgcgaaga gctgatcgcg gcgctgggag cgatccggcc gcgagcggct gcggtgccga 50340
tgcgctcgac ggtgacgggc ggggtgatcg cgggtccgga gctcggtgcg agctactggg 50400
cggacaacct tcggcagccg gtgcgcttcg ctgcggcggc gcaagcgctg ctggagggtg 50460
gccccgcgct gttcatcgag atgagcccgc acccgatcct ggtgccgccc ctggacgaga 50520
tccagacggc ggccgagcaa gggggcgctg cggtgggctc gctgcggcga gggcaggacg 50580
agcgcgcgac gctgctggag gcgctgggga cgctgtgggc gtccggctat ccggtgagct 50640
gggctcggct gttccccgcg ggcggcaggc gggttccgct gccgacctat ccctggcagc 50700
acgagcggta ctggatcgag gacagcgtgc atgggtcgaa gccctcgctg cggcttcggc 50760
agcttcgcaa cggcgccacg gaccatccgc tgctcggggc tccattgctc gtctcggcgc 50820
gacccggagc tcacttgtgg gagcaagcgc tgagcgacga gaggctatcc tacctttcgg 50880
aacatagggt ccatggcgaa gccgtgttgc ccagcgcggc gtatgtagag atggcgctcg 50940
ccgccggcgt agatctctat ggcacggcga cgctggtgct ggagcagctg gcgctcgagc 51000
gagccctcgc cgtgccctcc gaaggcggac gcatcgtgca agtggccctc agcgaagaag 51060
gtcccggtcg ggcctcattc caggtatcga gtcgtgagga ggcaggtagg agctgggtgc 51120
ggcacgccac ggggcacgtg tgtagcggcc agagctcagc ggtgggagcg ttgaaggaag 51180
ctccgtggga gattcaacgg cgatgtccga gcgtcctgtc gtcggaggcg ctctatccgc 51240
tgctcaacga gcacgccctc gactatggtc cctgcttcca gggcgtggag caggtgtggc 51300
tcggcacggg ggaggtgctc ggccgggtac gcttgccagg agacatggca tcctcaagtg 51360
gcgcctaccg gattcatccc gccttgttgg atgcatgttt tcaggtgctg acagcgctgc 51420
tcaccacgcc ggaatccatc gagattcgga ggcggctgac ggatctccac gaaccggatc 51480
tcccgcggtc cagggctccg gtgaatcaag cggtgagtga cacctggctg tgggacgccg 51540
cgctggacgg tggacggcgc cagagcgcga gcgtgcccgt cgacctggtg ctcggcagct 51600
tccatgcgaa gtgggaggtc atggagcgcc tcgcgcaggc gtacatcatc ggcactctcc 51660
gcatatggaa cgtcttctgc gctgctggag agcgtcacac gatagacgag ttgctcgtca 51720
ggcttcaaat ctctgtcgtc tacaggaagg tcatcaagcg atggatggaa caccttgtcg 51780
cgatcggcat ccttgtaggg gacggagagc atttgtgag ctctcagccg ctgccggagc 51840
ctgatttggc ggcggtgctc gaggaggccg ggagggtgtt cgccgacctc ccagtcctat 51900
ttgagtggtg caagtttgcc ggggaacggc tcgcggacgt attgaccggt aagacgctcg 51960
cgctcgagat cctcttccct ggtggctcgt tcgatatggc ggagcgaatc tatcgagatt 52020
cgcccatcgc ccgttactcg aacggcatcg tgcgcggtgt cgtcgagtcg gcggcgcggg 52080
tggtagcacc gtcgggaatg ttcagcatct tggagatcgg agcagggacg ggcgcgacca 52140
ccgccgccgt cctcccggtg ttgctgcctg accggacgga gtaccatttc accgatgttt 52200
ctccgctctt ccttgctcgc gcggagcaaa gatttcgaga ttatccattc ctgaagtatg 52260
gcattctgga tgtcgaccag gagccagctg gccagggata cgcacatcag aggtttgacg 52320
tcatcgtcgc ggccaatgtc atccatgcga cccgcgatat aagagccacg gcgaagcgtc 52380
tcctgtcgtt gctcgcgccc ggaggccttc tggtgctggt cgagggcaca gggcatccga 52440
tctggttcga tatcaccacg ggattgattg aggggtggca gaagtacgaa gatgatcttc 52500
gtatcgacca tccgctcctg cctgctcgga cctggtgtga cgtcctgcgc cgggtaggct 52560
ttgcggacgc cgtgagtctg ccaggcgacg gatctccggc ggggatcctc ggacagcacg 52620
tgatcctctc gcgcgcgccg ggcatagcag gagccgcttg tgacagctcc ggtgagtcgg 52680
cgaccgaatc gccggccgcg cgtgcagtac ggcaggaatg ggccgatggc tccgctgacg 52740
tcgtccatcg gatggcgttg gagaggatgt acttccaccg ccggccgggc cggcaggttt 52800
gggtccacgg tcgattgcgt accggtggag gcgcgttcac gaaggcgctc gctggagatc 52860
tgctcctgtt cgaagacacc gggcaggtcg tggcagaggt tcaggggctc cgcctgccgc 52920
agctcgaggc ttctgctttc gcgccgcggg acccgcggga agagtggttg tacgctttgg 52980
aatggcagcg caaagacccc ataccagagg ctccggcagc cgcgtcttct tcctccgcgg 53040
gggcttggct cgtgctgatg gaccagggcg ggacaggcgc tgcgctcgta tcgctgctgg 53100
aagggcgagg cgaggcgtgc gtgcgcgtca tcgcgggtac ggcatacgcc tgcctcgcgc 53160
cggggctgta tcaagtcgat ccggcgcagc cagatggctt tcataccctg ctccgcgatg 53220
cattcggcga ggaccggatt tgtcgcgcgg tagtgcatat gtggagcctt gatgcgacgg 53280
cagcagggga gagggcgaca gcggagtcgc ttcaggccga tcaactcctg ggagcctga 53340

gcgcgctttc tctggtgcag gcgctggtgc gccggaggtg gcgcaacatg ccgcggcttt 53400
ggctcttgac ccgcgccgtg catgcggtgg gcgcggagga cgcagcggcc tcggtggcgc 53460
aggcgccggt gtggggcctc ggtcggacgc tcgcgctcga gcatccagag ctgcggtgca 53520
cgctcgtgga cgtgaacccg gcgccgtctc cagaggacgc agccgcactg gcggtggagc 53580
tcggggcgag cgacagagag gaccaggtcg cattgcgctc ggatggccgc tacgtggcgc 53640
gcctcgtgcg gagctccttt tccggcaagc ctgctacgga ttgcggcatc cgggcggacg 53700
gcagctatgt gatcaccgat ggcatgggga gagtggggct ctcggtcgcg caatggatgg 53760
tgatgcaggg ggcccgccat gtggtgctcg tggatcgcgg cggcgcttcc gaggcatccc 53820
gggatgccct ccggtccatg gccgaggctg gcgcggaggt gcagatcgtg gaggccgacg 53880
tggctcggcg cgacgatgtc gctcggctcc tctcgaagat cgaaccgtcg atgccgccgc 53940
ttcgggggat cgtgtacgtg gacgggacct tccagggcga ctcctcgatg ctggagctgg 54000
atgcccgtcg cttcaaggag tggatgtatc ccaaggtgct cggagcgtgg aacctgcacg 54060
cgctgaccag ggatagatcg ctggacttct tcgtcctgta ttcctcgggc acctcgcttc 54120
tgggcttgcc aggacagggg agccgcgccg ccggtgacgc cttcttggac gccatcgcgc 54180
atcaccggtg caaggtgggc cttacagcga tgagcatcaa ctggggattg ctctccgaag 54240
catcatcgcc ggcgaccccg aacgacggcg gagcacggct cgaataccgg gggatggaag 54300
gcctcacgct ggagcaggga gcggcggcgc tcgggcgctt gctcgcacga cccagggcgc 54360
aggtaggggt gatgcggctg aatctgcgcc agtggttgga gttctatccc aacgcggccc 54420
gattggcgct gtgggcggag ctgctgaagg agcgtgaccg cgccgaccga ggcgcgtcga 54480
acgcgtcgaa cctgcgcgag gcgctgcaga gcgccaggcc cgaagatcgt cagttgattc 54540
tggagaagca cttgagcgag ctgttggggc gggggctgcg ccttccgccg gagaggatcg 54600
agcggcacgt gccgttcagc aatctcggca tggactcgct gataggcctg gagctccgca 54660
accgcatcga ggccgcgctc ggcatcaccg tgccggcgac cctgctatgg acctacccta 54720
acgtagcagc tctgagcggg agcttgctag acattctgtt tccgaatgcc ggcgcgaccc 54780
acgctccggc caccgagcgg gagaagagct tcgagaacga tgccgcagat ctcgaggctc 54840
tgcggggcat gacggacgag cagaaggacg cgttgctcgc cgaaaagctg gcgcagctcg 54900
cgcagatcgt tggtgagtaa gggaccgagg gagtatggcg accacgaatg ccgggaagct 54960
tgagcatgcc cttctgctca tggacaagct tgcgaaaaag aacgcgtctt tggagcaaga 55020
gcggaccgag ccgatcgcca tcgtaggcat tggctgccgc ttccccggcg gagcggacac 55080
tccggaggca ttctgggagc tgctcgactc aggccgagac gcggtccagc cgctcgaccg 55140
gcgctgggcg ctggtcggcg tccatcccag cgaggaggtg ccgcgctggg ccggactgct 55200
caccgaggcg gtggacggct tcgacgccgc gttctttggc acctcgcctc gggaggcgcg 55260
gtcgctcgat cctcagcaac gcctgctgct ggaggtcacc tgggaagggc tcgaggacgc 55320
cggcatcgca ccccagtccc tcgacggcag ccgcaccggg gtgttcctgg gcgcatgcag 55380
cagcgactac tcgcataccg ttgcgcaaca gcggcgcgag gagcaggacg catacgacat 55440
caccggcaat acgctcagcg tcgccgccgg acggttgtct tatacgctag ggctgcaggg 55500
accctgcctg accgtcgaca cggcctgctc gtcgtcgctc gtggccatcc accttgcctg 55560
ccgcagcctg cgcgctcgcg agagcgatct cgcgctggcg ggaggcgtca acatgctcct 55620
ttcgtccaag acgatgataa tgctggggcg catccaggcg ctgtcgcccg atggccactg 55680
ccggacattc gacgcctcgg ccaacgggtt cgtccgtggg gagggctgcg gtatggtcgt 55740
gctcaaacgg ctctccgacg cccagcgaca cggcgatcgg atctgggctc tgatccgggg 55800
ttcggccatg aatcaggatg gccggtcgac agggttgatg gcacccaatg tgctcgctca 55860
ggaggcgctc ttgcgcgagg cgctgcagag cgctcgcgtc gacgccgggg ccatcggtta 55920
tgtcgagacc cacggaacgg ggacctcgct cggcgacccg atcgaggtcg aggcgctgcg 55980
tgccgtgttg ggccggcgc gggccgatgg gagccgctgc gtgctgggcg cagtgaagac 56040
aaacctcggc cacctggagg gcgctgcagg cgtggcgggt ttgatcaagg cggcgctggc 56100
tctgcaccac gaactgatcc cgcgaaacct ccatttccac acgctcaatc cgcggatccg 56160
gatcgagggg accgcgctcg cgctggcgac ggagccggtg ccgtggccgc gggcgggccg 56220
accgcgcttc gcgggggtga gcgcgttcgg cctcagcggc accaacgtcc atgtcgtgct 56280
ggaggaggcg ccggccacgg tgctcgcacc ggcgacgccg gggcgctcag cggagctttt 56340
ggtgctgtcg gcgaagagcg ccgccgcgct ggacgcacag gcggcgcggc tctcagcgca 56400
catcgccgcg tacccggagc agggtctcgg agacgtcgcg ttcagcctgg tatcgacgcg 56460
tagcccgatg gagcaccggc tcgcggtggc ggcgacctcg cgcgaggcgc tgcgaagcgc 56520
gctggaggtt gcggcgcagg ggcagacccc ggcaggcgcg gcgcgcggca gggccgcttc 56580
ctcgcccggc aagctcgcct tcctgttcgc cgggcagggc gcgcaggtgc cgggcatggg 56640
ccgtgggttg tgggaggcgt ggccggcgtt ccgcgagacc ttcgaccggt gcgtcacgct 56700
cttcgaccgg gagctccatc agccgctctg cgaggtgatg tgggccgagc cgggcagcag 56760
caggtcgtcg ttgctggacc agacggcgtt cacccagccg gcgctctttg cgctggagta 56820
cgcgctggcc gcgctcttcc ggtcgtgggg cgtggagccg gagctcgtcg ctggccatag 56880
cctcggcgag ctggtggccg cctgcgtggc gggtgtgttc tccctcgagg acgccgtgcg 56940
cttggtggtc gcgcgcggcc ggttgatgca ggcgctgccg gccggcggcg cgatggtatc 57000
gatcgccgcg ccggaggccg acgtggctgc cgcggtggcg ccgcacgcag cgttggtgtc 57060
gatcgcggca gtcaatgggc cggagcaggt ggtgatcgcg ggcgccgaga aattcgtgca 57120
gcagatcgcg gcggcgttcg cggcgcgggg ggcgcgaacc aaaccgctgc atgtctcgca 57180
cgcgttccac tcgccgctca tggatccgat gctggaggcg ttccggcggg tgactgagtc 57240

ggtgacgtac cggcggcctt cgatcgcgct ggtgagcaac ctgagcggga agccctgcac 57300
cgatgaggtg agcgcgccgg gttactgggt gcgtcacgcg cgagaggcgg tgcgcttcgc 57360
ggacggagtg aaggcgctgc acgcggccgg tgcgggcctc ttcgtcgagg tggggccgaa 57420
gccgacgctg ctcggccttg tgccggcctg cctgccggat gccaggccgg tgctgctccc 57480
agcgtcgcgc gccgggcgtg acgaggctgc gagcgcgcta gaggcgctgg gtgggttctg 57540
ggtcgtcggt ggatcggtca cctggtcggg tgtcttccct tcgggcggac ggcgggtacc 57600
gctgccaacc tatccctggc agcgcgagcg ttactggatc gaagcgccgg tcgatcgtga 57660
ggcggacggc accggccgtg ctcgggcggg gggccacccc cttctgggtg aagtcttttc 57720
cgtgtcgacc catgccggtc tgcgcctgtg ggagacgacg ctggaccgaa agcggctgcc 57780
gtggctcggc gagcaccggg cgcagggggga ggtcgtgttt cctggcgccg ggtacctgga 57840
gatggcgctg tcgtcggggg ccgagatctt gggcgatgga ccgatccagg tcacggatgt 57900
ggtgctcatc gagacgctga ccttcgcggg cgatacggcg gtaccggtcc aggtggtgac 57960
gaccgaggag cgaccgggac ggctgcggtt ccaggtagcg agtcgggagc cgggggaacg 58020
tcgcgcgccc ttccggatcc acgcccgcgg cgtgctgcgc cggatcgggc gcgtcgagac 58080
cccggcgagg tcgaacctcg ccgccctgcg cgcccggctt catgccgccg tgcccgctgc 58140
ggctatctat ggtgcgctcg ccgagatggg gcttcaatac ggcccggcgt tgcggggggct 58200
cgccgagctg tggcggggtg agggcgaggc gctgggcagg gtgagactgc ctgaggccgc 58260
cggctccgcg acagcctacc agctgcatcc ggtgctgctg gacgcgtgcg tccaaatgat 58320
tgttggcgcg ttcgccgatc gcgatgaggc gacgccgtgg gcgccggtgg aggtgggctc 58380
ggtgcggctg ttccagcggt ctcctgggga gctatggtgc catgcgcgcg tcgtgagcga 58440
tggtcaacag gcctccagcc ggtggagcgc cgactttgag ttgatggacg gtacgggcgc 58500
ggtggtcgcc gagatctccc ggctggtggt ggagcggctt gcgagcggtg tacgccggcg 58560
cgacgcagac gactggttcc tggagctgga ttgggagccc gcggcgctcg gtgggcccaa 58620
gatcacagcc ggccggtggc tgctgctcgg cgagggtggt gggctcgggc gctcgttgtg 58680
ctcggcgctg aaggccgccg gccatgtcgt cgtccacgcc gcgggggacg acacgagcac 58740
tgcaggaatg cgcgcgctcc tggccaacgc gttcgacggc caggccccga cggccgtggt 58800
gcacctcagc agcctcgacg gggcggccca gctcggcccg gggctcgggg cgcagggcgc 58860
gctcgacgcg ccccggagcc cagatgtcga tgccgatgcc ctcgaatcgg cgctgatgcg 58920
tggttgcgac agcgtgctct ccctggtgca agcgctggtc ggcatggacc tccgaaacgc 58980
gccgcggctg tggctcttga cccgcggggc tcaggcggcc gccgccggcg atgtctccgt 59040
ggtgcaagcg ccgctgttgg ggctgggccg caccatcgcc ttggagcacg ccgagctgcg 59100
ctgtatcagc gtcgacctcg atccagccga gcctgaaggg gaagccgatg ctttgctggc 59160
cgagctactt gcagatgatg ccgaggagga ggtcgcgctg cgcggtggcg accggctcgt 59220
tgcgcggctc gtccaccggc tgcccgacgc tcagcgccgg gagaaggtcg agcccgccgg 59280
tgacaggccg ttccggctag agatcgatga acccggcgcg ctggaccaac tggtgctccg 59340
agccacgggg cggcgcgctc ctggtccggg cgaggtcgag atctccgtcg aagcggcggg 59400
gctcgactcc atcgacatcc agctggcgtt gggcgttgct cccaatgatc tgcctggaga 59460
agaaatcgag ccgttggtgc tcggaagcga gtgcgccggg cgcatcgtcg ctgtgggcga 59520
gggcgtgaac ggccttgtgg tgggccagcc ggtgatcgcc cttgcggcgg gagtatttgc 59580
tacccatgtc accacgtcgg ccacgctggt gttgcctcgg cctctggggc tctcggcgac 59640
cgaggcggcc gcgatgcccc tcgcgtattt gacggcctgg tacgccctcg acaaggtcgc 59700
ccacctgcag gcgggggagc gggtgctgat ccatgcggag gccggtggtg tcggtctttg 59760
cgcggtgcga tgggcgcagc gcgtgggcgc cgaggtgtat gcgaccgccg acacgcccga 59820
gaaccgtgcc tacctggagt cgctgggcgt gcggtacgtg agcgattccc gctcgggccg 59880
gttcgtcaca gacgtgcatg catggacgga cggcgagggt gtggacgtcg tgctcgactc 59940
gctttcgggc gagcgcatcg acaagagcct catggtcctg cgcgcctgtg gtcgccttgt 60000
gaagctgggc aggcgcgacg actgcgccga cacgcagcct gggctgccgc cgctcctacg 60060
gaatttttcc ttctcgcagg tggacttgcg gggaatgatg ctcgatcaac cggcgaggat 60120
ccgtgcgctc ctcgacgagc tgttcgggtt ggtcgcagcc ggtgccatca gcccactggg 60180
gtcggggttg cgcgttggcg gatccctcac gccaccgccg gtcgagacct tcccgatctc 60240
tcgcgcagcc gaggcattcc ggaggatggc gcaaggacag catctcggga agctcgtgct 60300
cacgctggac gacccggagg tgcggatccg cgctccggcc gaatccagcg tcgccgtccg 60360
cgcggacggc acctaccttg tgaccggcgg tctgggtggc ctcggtctgc gcgtggccgg 60420
atggctggcc gagcggggcg cggggcaact ggtgctggtg ggccgctccg gtgcggcgag 60480
cgcagagcag cgagccgccg tggcggcgct ggaggcccac ggcgcgcgcg tcacggtggc 60540
gaaagcggac gtcgccgatc ggtcacagat cgagcgggtc ctccgcgagg ttaccgcgtc 60600
ggggatgccg ctgcggggtg tcgtgcatgc ggcaggtctc gtggatgacg ggctgctgat 60660
gcagcagact ccggcgcggt tccgcacggt gatgggacct aaggtccagg gggccttgca 60720
cttgcacacg ctgacacgcg aagcgcctct ttccttcttc gtgctgtacg cttctgcagc 60780
tgggcttttc ggctcgccag gccagggcaa ctatgccgca gccaacgcgt tcctcgacgc 60840
cctttcgcat caccgaaggg cgcagggcct gccggcgctg agcatcgact ggggcatgtt 60900
cacggaggtg gggatggccg ttgcgcaaga aaaccgtggc gcgcggcaga tctctcgcgg 60960
gatgcggggc atcacccccg atgagggtct gtcagctctg gcgcgcttgc tcgagggtga 61020
tcgcgtgcag acgggggtga taccgatcac tccgcggcag tgggtggagt tctacccggc 61080
aacagcggcc tcacggaggt tgtcgcggct ggtgaccacg cagcgcgcgg tcgctgatcg 61140

gaccgccggg gatcgggacc tgctcgaaca gcttgcgtcg gctgagccga gcgcgcgggc 61200
ggggctgctg caggacgtcg tgcgcgtgca ggtctcgcat gtgctgcgtc tccctgaaga 61260
caagatcgag gtggatgccc cgctctcgag catgggcatg gactcgctga tgagcctgga 61320
gctgcgcaac cgcatcgagg ctgcgctggg cgtcgccgcg cctgcagcct tggggtggac 61380
gtacccaacg gtagcagcga taacgcgctg gctgctcgac gacgccctcg tcgtccggct 61440
tggcggcggg tcggacacgg acgaatcgac ggcgagcgcc ggttcgttcg tccacgtcct 61500
ccgctttcgt cctgtcgtca agccgcgggc tcgtctcttc tgttttcacg gttctggcgg 61560
ctcgcccgag ggcttccgtt cctggtcgga gaagtctgag tggagcgatc tggaaatcgt 61620
ggccatgtgg cacgatcgca gcctcgcctc cgaggacgcg cctggtaaga agtacgtcca 61680
agaggcggcc tcgctgattc agcactatgc agacgcaccg tttgcgttag tagggttcag 61740
cctgggtgtc cggttcgtca tggggacagc cgtggagctc gccagtcgtt ccggcgcacc 61800
ggctccgctg gccgtcttca cgttgggcgg cagcttgatc tcttcttcag agatcacccc 61860
ggagatggag accgatataa tagccaagct cttcttccga aatgccgcgg gtttcgtgcg 61920
atccacccaa caagtccagg ccgatgctcg cgcagacaag gtcatcacag acaccatggt 61980
ggctccggcc cccggggact cgaaggagcc gcccgtgaag atcgcggtcc ctatcgtcgc 62040
catcgccggc tcggacgatg tgatcgtgcc tccgagcgac gttcaggatc tacaatctcg 62100
caccacggag cgcttctata tgcatctcct tcccggagat cacgaatttc tcgtcgatcg 62160
agggcgcgag atcatgcaca tcgtcgactc gcatctcaat ccgctgctcg ccgcgaggac 62220
gacgtcgtca ggccccgcgt tcgaggcaaa atgatggcag cctccctcgg gcgcgcgaga 62280
tggttgggag cagcgtgggc gctggcggcc ggcggcaggc cgcggaggcg catgagcctt 62340
cctggacgtt tgcagtatag gagattttat gacacaggag caagcgaatc agagtgagac 62400
gaagcctgct ttcgacttca agccgttcgc gcctgggtac gcggaggacc cgttccccgc 62460
gatcgagcgc ctgagagagg caaccccat cttctactgg gatgaaggcc gctcctgggt 62520
cctcacccga taccacgacg tgtcggcggt gttccgcgac gaacgcttcg cggtcagtcg 62580
agaagagtgg gaatcgagcg cggagtactc gtcggccatt cccgagctca gcgatatgaa 62640
gaagtacgga ttgttcgggc tgccgccgga ggatcacgct cgggtccgca agctcgtcaa 62700
cccgtcgttt acgtcacgcg ccatcgacct gctgcgcgcc gaaatacagc gcaccgtcga 62760
ccagctgctc gatgctcgct ccggacaaga ggagttcgac gttgtgcggg attacgcgga 62820
gggaatcccg atgcgcgcga tcagcgctct gttgaaggtt ccggccgagt gtgacgagaa 62880
gttccgtcgc ttcggctcgg cgactgcgcg cgcgctcggc gtgggtttgg tgccccaggt 62940
cgatgaggag accaagaccc tggtcgcgtc cgtcaccgag gggctcgcgc tgctccatga 63000
cgtcctcgat gagcggcgca ggaacccgct cgaaaatgac gtcttgacga tgctgcttca 63060
ggccgaggcc gacggcagca ggctgagcac gaaggagctg gtcgcgctcg tgggtgcgat 63120
tatcgctgct ggcaccgata ccacgatcta ccttatcgcg ttcgctgtgc tcaacctgct 63180
gcggtcgccc gaggcgctcg agctggtgaa ggccgagccc gggctcatga ggaacgcgct 63240
cgatgaggtg ctccgcttcg acaatatcct cagaatagga actgtgcgtt tcgccaggca 63300
ggacctggag tactgcgggg catcgatcaa gaaaggggag atggtctttc tcctgatccc 53360
gagcgccctg agagatggga ctgtattctc caggccagac gtgtttgatg tgcgacggga 63420
cacgggcgcg agcctcgcgt acggtagagg cccccatgtc tgccccgggg tgtcccttgc 63480
tcgcctcgag gcggagatcg ccgtgggcac catcttccgt aggttccccg agatgaagct 63540
gaaagaaact cccgtgtttg gataccaccc cgcgttccgg aacatcgaat cactcaacgt 63600
catcttgaag ccctccaaag ctggatagct cgcgggggta tcgcttcccg aacctcattc 63660
cctcatgata cagctcgcgc gcgggtgctg tctgccgcgg gtgcgattcg atccagcgga 63720
caagcccatt gtcagcgcgc gaagatcgaa tccacggccc ggagaagagc ccgtccgggt 63780
gacgtcggaa gaagtgccgg gcgccgccct gggagcgcaa agctcgctcg ttcgcgctca 63840
gcacgccgct cgtcatgtcc ggccctgcac ccgcgccgag gagccgcccg ccctgatgca 63900
cggcctcacc gagcggcagg ttctgctctc gctcgtcgcc ctcgcgctcg tcctcctgac 63960
cgcgcgcgcc ttcggcgagc tcgcgcggcg gctgcgccag cccgaggtgc tcggcgagct 64020
cttcggcggc gtggtgctgg gcccgtccgt cgtcggcgcg ctcgctcctg ggttccatcg 64080
agtcctcttc caggatccgg cggtcggggt cgtgctctcc ggcatctcct ggataggcgc 64140
gctcgtcctg ctgctcatgg cgggtatcga ggtcgatgtg agcatcctgc gcaaggaggc 64200
gcgccccggg gcgctctcgg cgctcggcgc gatcgcgccc ccgctgcgca cgccggggcc 64260
gctggtgcag cgcatgcagg gcgcgttcac gtgggatctc gacgtctcgc cgcgacgctc 64320
tgcgcaagcc tgagcctcgg cgcctgctcg tacacctcgc cggtgctcgc tccgcccgcg 64380
gacatccggc cgcccgccgc ggcccagctc gagccggact cgccggatga cgaggccgac 64440
gaggccgacg aggcgctccg cccgttccgc gacgcgatcg ccgcgtactc ggaggccgtt 64500
cggtgggcgg aggcggcgca gcggccgcgg ctggagagcc tcgtgcggct cgcgatcgtg 64560
cggctgggca aggcgctcga caaggtccct ttcgcgcaca cgacggccgg cgtctcccag 64620
atcgccggca gactccagaa cgatgcggtc tggttcgatg tcgccgcccg gtacgcgagc 64680
ttccgcgcgg cgacggagca cgcgctccgc gacgcggcgt cggccatgga ggcgctcgcg 64740
gccggcccgt accgcggatc gagccgcgtg tccgctgccg taggggagtt tcgggggag 64800
gcggcgcgcc ttcaccccgc ggaccgtgta cccgcgtccg accagcagat cctgaccgcg 64860
ctgcgcgcag ccgagcgggc gctcatcgcg ctctacactg cgttcgcccg tgaggagtga 64920
gcctctctcg ggcgcagccg agcggcggcg tgccggtggt tccctcttcg caaccatgac 64980
cggagccgcg ctcggtccgc gcagcggcta gcgcgcgtcg cggcagagat cgctggagcg 65040

acaggcgacg acccgcccga gggtgtcgaa cggattgccg cagccctcat tgcggatccc 65100
ctccagacac tcgttcagct gcttggcgtc gatgccgcct gggcactcgc cgaaggtcag 65160
ctcgtcgcgc cactcggatc ggatcttgtt cgagcacgcg tccttgctcg aatactcccg 65220
gtcttgtccg atgttgttgc accgcgcctc gcggtcgcac cgcgccgcca cgatgctatc 65280
gacggcgctg ccgactggca ccggcgcctc gccctgcgcg ccacccgggg tttgcgcctc 65340
cccgcctgac cgcttttcgc cgccgcacgc cgcgagcagg ctcattcccg acaccgagat 65400
caggcccacg accagcttcc cagcaatctt ttgcatggct tcccctccct cacgacacgt 65460
cacatcagag actctccgct cggctcgtcg gttcgacagc cggcgacggc cacgagcaga 65520
accgtccccg accagaacag ccgcatgcgg gtttctcgca acatgccccg acatccttgc 65580
gactagcgtg cctccgctcg tgccgagatc ggctgtcctg tgcgacggca atatcctgcg 65640
atcggccggg caggaggtac cgacacgggc gccgggcggg aggtgccgcc acgggctcga 65700
aatgtgctgc ggcaggcgcc tccatgcccg cagccgggaa cgcggcgccc ggccagcctc 65760
ggggtgacgc cgcaaacggg agatgctccc ggagaggcgc cgggcacagc cgagcgccgt 65820
caccaccgtg cgcactcgtg agctccagct cctcggcata gaagagaccg tcactcccgg 65880
tccgtgtagg cgatcgtgct gatcagcgcg ttctccgcct gacgcgagtc gagccgggta 65940
tgctgcacga caatgggaac gtccgattcg atcacgctgg catagtccgt atcgcgcggg 66000
atcggctcgg gttcggtcag atcgttgaac cggacgtgcc gggtgcgcct cgctgggacg 66060
gtcacccggt acggcccggc ggggtcgcgg tcgctgaagt agacggtgat ggcgacctgc 66120
gcgtcccggt ccgacgcatt caacaggcag gccgtctcat ggctcgtcat ctgcggctcg 66180
ggtccgttgc tccggcctgg gatgtagccc tctgcgattg cccagcgcgt ccgcccgatc 66240
ggcttctcca tatgtcctcc ctgctggctc ctctttggct gcctccctct gctgtccagg 66300
agcgacggcc tcttctcccg acgcgctcgg ggatccatgg ctgaggatcc tcgccgagcg 66360
ctccttgccg accggcgcgc cgagcgccga cgggctttga aagcacgcga ccggacacgt 66420
gatgccggcg cgacgaggcc gccccgcgtc tgatcccgat cgtgacatcg cgacgtccgc 66480
cggcgcctct gcaggccggc ctgagcgttg cgcggtcatg gtcgtcctcg cgtcaccgcc 66540
acccgccgat tcacatccca ccgcggcacg acgcttgctc aaaccgcggc gagacggccg 66600
ggcggctgtg gtaccggcca gcccggacgc gaggcccgag agggacagtg ggtccgccgt 66660
gaagcagtga ggcgatcgag gtggcagatg aaacacgttg acacgggccg acgagtcggc 66720
cgccggatag ggctcacgct cggtctcctc gcgagcatgg cgctcgccgg ctgtggcggc 66780
ccgagcgaga aaatcgtgca gggcacgcgg ctcgcgcccg gcgccgatgc gcacgtcgcc 66840
gccgacgtcg accccgacgc cgcgaccacg cggctggcgg tggacgtcgt tcacctctcg 66900
ccgcccgagc gcatcgaggc cggcagcgag cggttcgtcg tctggcagcg tccgagctcc 66960
gagtccccgt ggcaacgggt cggagtgctc gactacaacg ctgccagccg aagaggcaag 67020
ctggccgaga cgaccgtgcc gcatgccaac ttcgagctgc tcatcaccgt cgagaagcag 67080
agcagccctc agtctccatc ttctgccgcc gtcatcgggc cgacgtccgt cgggtaacat 67140
cgcgctatca gcagcgctga gcccgccagc aggccccaga gccctgcctc gatcgccttc 67200
tccatcatat catccctgcg tactcctcca gcgacggccg cgtcgaagca accgccgtgc 67260
cggcgcggct ctacgtgcgc gacaggagag cgtcctggcg cggcctgcgc atcgctggaa 67320
ggatcggcgg agcatggaga aagaatcgag gatcgcgatc tacggcgcca tcgcagccaa 67380
cgtggcgatc gcggcggtca agttcatcgc cgccgccgtg accggcagct cggcgatgct 67440
ctccgagggc gtgcactccc tcgtcgatac tgcagacggg ctcctcctcc tgctcggcaa 67500
gcaccggagc gcacgcccgc ccgacgccga gcatccgttc ggccacggca aggagctcta 67560
tttctggacg ctgatcgtcg ccatcatgat cttcgccgcg ggcggcggcg tctcgatcta 67620
cgaagggatc ttgcacctct tgcacccgcg ccagatcgag gatccgacgt ggaactacgt 67680
cgtcctcggc gcagcggccg tcttcgaggg gacgtcgctc atcatctcga tccacgagtt 67740
caagaagaag gacggacagg gctacctcgc ggcgatgcgg tccagcaagg acccgacgac 67800
gttcacgatc gtcctggagg actccgcggc gctcgccggg ctcaccatcg ccttcctcgg 67860
cgtctggctc gggcaccgcc tgggaaaccc ctacctcgac ggcgcggcgt cgatcggcat 67920
cggcctcgtg ctcgccgcgg tcgcggtctt cctcgccagc cagagccgtg ggctcctcgt 67980
gggggagagc gcggacaggg agctcctcgc cgcgatccgc gcgctcgcca gcgcagatcc 68040
tggcgtgtcg gcggtggggc ggcccctgac gatgcacttc ggtccgcacg aagtcctggt 68100
cgtgctgcgc atcgagttcg acgccgcgct cacggcgtcc ggggtcgcgg aggcgatcga 68160
gcgcatcgag acccggatac ggagcgagcg acccgacgtg aagcacatct acgtcgaggc 68220
caggtcgctc caccagcgcg cgagggcgtg acgcgccgtg gagagaccgc gcgcggcctc 68280
cgccatcctc cgcggcgccc gggctcaggt ggccctcgca gcagggcgcg cctggcgggc 68340
aaaccgtgca gacgtcgtcc ttcgacgcga ggtacgctgg ttgcaagtcg tcacgccgta 68400
tcgcgaggtc cggcagcgcc ggagcccggg cgggccgggc gcacgaaggc gcggcgagcg 68460
caggcttcga gcgggggcgac gtcatgagga aggccagggc gcatggggcg atgctcggcg 68520
ggcgagatga cggctggcgt cgcggcctcc ccggcgccgg cgcgcttcgc gccgcgctcc 68580
agcgcggtcg ctcgcgcgat ctcgcccggc gccggctcat cgcctccgtg tccctcgccg 68640
gcggcgccag catggcggtc gtctcgctgt tccagctcgg gatcatcgag cgcctgcccg 68700
atcctccgct tccagggttc gattcggcca aggtgacgag ctccgatatc 68750

<210> 2
<211> 1421

<212> PRT
<213> Sorangium cellulosum

<400> 2
```
Val Ala Asp Arg Pro Ile Glu Arg Ala Ala Glu Asp Pro Ile Ala Ile
1               5                   10                  15

Val Gly Ala Ser Cys Arg Leu Pro Gly Gly Val Ile Asp Leu Ser Gly
            20                  25                  30

Phe Trp Thr Leu Leu Glu Gly Ser Arg Asp Thr Val Gly Arg Val Pro
        35                  40                  45

Ala Glu Arg Trp Asp Ala Ala Ala Trp Phe Asp Pro Asp Pro Asp Ala
    50                  55                  60

Pro Gly Lys Thr Pro Val Thr Arg Ala Ser Phe Leu Ser Asp Val Ala
65                  70                  75                  80

Cys Phe Asp Ala Ser Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Arg
                85                  90                  95

Met Asp Pro Ala His Arg Leu Leu Leu Glu Val Cys Trp Glu Ala Leu
            100                 105                 110

Glu Asn Ala Ala Ile Ala Pro Ser Ala Leu Val Gly Thr Glu Thr Gly
        115                 120                 125

Val Phe Ile Gly Ile Gly Pro Ser Glu Tyr Glu Ala Ala Leu Pro Gln
    130                 135                 140

Ala Thr Ala Ser Ala Glu Ile Asp Ala His Gly Gly Leu Gly Thr Met
145                 150                 155                 160

Pro Ser Val Gly Ala Gly Arg Ile Ser Tyr Ala Leu Gly Leu Arg Gly
                165                 170                 175

Pro Cys Val Ala Val Asp Thr Ala Tyr Ser Ser Ser Leu Val Ala Val
            180                 185                 190

His Leu Ala Cys Gln Ser Leu Arg Ser Gly Glu Cys Ser Thr Ala Leu
        195                 200                 205

Ala Gly Gly Val Ser Leu Met Leu Ser Pro Ser Thr Leu Val Trp Leu
    210                 215                 220

Ser Lys Thr Arg Ala Leu Ala Arg Asp Gly Arg Cys Lys Ala Phe Ser
225                 230                 235                 240

Ala Glu Ala Asp Gly Phe Gly Arg Gly Glu Gly Cys Ala Val Val Val
                245                 250                 255

Leu Lys Arg Leu Ser Gly Ala Arg Ala Asp Gly Asp Arg Ile Leu Ala
            260                 265                 270

Val Ile Arg Gly Ser Ala Ile Asn His Asp Gly Ala Ser Ser Gly Leu
        275                 280                 285

Thr Val Pro Asn Gly Ser Ser Gln Glu Ile Val Leu Lys Arg Ala Leu
    290                 295                 300

Ala Asp Ala Gly Cys Ala Ala Ser Ser Val Gly Tyr Val Glu Ala His
305                 310                 315                 320

Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile Glu Ile Gln Ala Leu Asn
```

```
                325                     330                     335

Ala Val Tyr Gly Leu Gly Arg Asp Val Ala Thr Pro Leu Leu Ile Gly
            340                     345                     350

Ser Val Lys Thr Asn Leu Gly His Pro Glu Tyr Ala Ser Gly Ile Thr
        355                     360                     365

Gly Leu Leu Lys Val Val Leu Ser Leu Gln His Gly Gln Ile Pro Ala
    370                     375                     380

His Leu His Ala Gln Ala Leu Asn Pro Arg Ile Ser Trp Gly Asp Leu
385                     390                     395                     400

Arg Leu Thr Val Thr Arg Ala Arg Thr Pro Trp Pro Asp Trp Asn Thr
                405                     410                     415

Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Met Ser Gly Thr Asn Ala
            420                     425                     430

His Val Val Leu Glu Glu Ala Pro Ala Ala Thr Cys Thr Pro Pro Ala
        435                     440                     445

Pro Glu Arg Pro Ala Glu Leu Leu Val Leu Ser Ala Arg Thr Ala Ser
    450                     455                     460

Ala Leu Asp Ala Gln Ala Ala Arg Leu Arg Asp His Leu Glu Thr Tyr
465                     470                     475                     480

Pro Ser Gln Cys Leu Gly Asp Val Ala Phe Ser Leu Ala Thr Thr Arg
                485                     490                     495

Ser Ala Met Glu His Arg Leu Ala Val Ala Ala Thr Ser Arg Glu Gly
            500                     505                     510

Leu Arg Ala Ala Leu Asp Ala Ala Ala Gln Gly Gln Thr Ser Pro Gly
        515                     520                     525

Ala Val Arg Ser Ile Ala Asp Ser Ser Arg Gly Lys Leu Ala Phe Leu
    530                     535                     540

Phe Thr Gly Gln Gly Ala Gln Thr Leu Gly Met Gly Arg Gly Leu Tyr
545                     550                     555                     560

Asp Val Trp Ser Ala Phe Arg Glu Ala Phe Asp Leu Cys Val Arg Leu
                565                     570                     575

Phe Asn Gln Glu Leu Asp Arg Pro Leu Arg Glu Val Met Trp Ala Glu
            580                     585                     590

Pro Ala Ser Val Asp Ala Ala Leu Leu Asp Gln Thr Ala Phe Thr Gln
        595                     600                     605

Pro Ala Leu Phe Thr Phe Glu Tyr Ala Leu Ala Ala Leu Trp Arg Ser
    610                     615                     620

Trp Gly Val Glu Pro Glu Leu Val Ala Gly His Ser Ile Gly Glu Leu
625                     630                     635                     640

Val Ala Ala Cys Val Ala Gly Val Phe Ser Leu Glu Asp Ala Val Phe
                645                     650                     655

Leu Val Ala Ala Arg Gly Arg Leu Met Gln Ala Leu Pro Ala Gly Gly
            660                     665                     670
```

Ala Met Val Ser Ile Glu Ala Pro Glu Ala Asp Val Ala Ala Ala Val
675 680 685

Ala Pro His Ala Ala Ser Val Ser Ile Ala Ala Val Asn Ala Pro Asp
690 695 700

Gln Val Val Ile Ala Gly Ala Gly Gln Pro Val His Ala Ile Ala Ala
705 710 715 720

Ala Met Ala Ala Arg Gly Ala Arg Thr Lys Ala Leu His Val Ser His
725 730 735

Ala Phe His Ser Pro Leu Met Ala Pro Met Leu Glu Ala Phe Gly Arg
740 745 750

Val Ala Glu Ser Val Ser Tyr Arg Arg Pro Ser Ile Val Leu Val Ser
755 760 765

Asn Leu Ser Gly Lys Ala Cys Thr Asp Glu Val Ser Ser Pro Gly Tyr
770 775 780

Trp Val Arg His Ala Arg Glu Val Val Arg Phe Ala Asp Gly Val Lys
785 790 795 800

Ala Leu His Ala Ala Gly Ala Gly Thr Phe Val Glu Val Gly Pro Lys
805 810 815

Ser Thr Leu Leu Gly Leu Val Pro Ala Cys Met Pro Asp Ala Arg Pro
820 825 830

Ala Leu Leu Ala Ser Ser Arg Ala Gly Arg Asp Glu Pro Ala Thr Val
835 840 845

Leu Glu Ala Leu Gly Gly Leu Trp Ala Val Gly Gly Leu Val Ser Trp
850 855 860

Ala Gly Leu Phe Pro Ser Gly Gly Arg Arg Val Pro Leu Pro Thr Tyr
865 870 875 880

Pro Trp Gln Arg Glu Arg Tyr Trp Ile Asp Thr Lys Ala Asp Asp Ala
885 890 895

Ala Arg Gly Asp Arg Arg Ala Pro Gly Ala Gly His Asp Glu Val Glu
900 905 910

Glu Gly Gly Ala Val Arg Gly Gly Asp Arg Arg Ser Ala Arg Leu Asp
915 920 925

His Pro Pro Pro Glu Ser Gly Arg Arg Glu Lys Val Glu Ala Ala Gly
930 935 940

Asp Arg Pro Phe Arg Leu Glu Ile Asp Glu Pro Gly Val Leu Asp His
945 950 955 960

Leu Val Leu Arg Val Thr Glu Arg Arg Ala Pro Gly Leu Gly Glu Val
965 970 975

Glu Ile Ala Val Asp Ala Ala Gly Leu Ser Phe Asn Asp Val Gln Leu
980 985 990

Ala Leu Gly Met Val Pro Asp Asp Leu Pro Gly Lys Pro Asn Pro Pro
995 1000 1005

Leu Leu Leu Gly Gly Glu Cys Ala Gly Arg Ile Val Ala Val Gly Glu
1010 1015 1020

Gly Val Asn Gly Leu Val Val Gly Gln Pro Val Ile Ala Leu Ser Ala
1025 1030 1035 1040

Gly Ala Phe Ala Thr His Val Thr Thr Ser Ala Ala Leu Val Leu Pro
1045 1050 1055

Arg Pro Gln Ala Leu Ser Ala Ile Glu Ala Ala Ala Met Pro Val Ala
1060 1065 1070

Tyr Leu Thr Ala Trp Tyr Ala Leu Asp Arg Ile Ala Arg Leu Gln Pro
1075 1080 1085

Gly Glu Arg Val Leu Ile His Ala Ala Thr Gly Gly Val Gly Leu Ala
1090 1095 1100

Ala Val Gln Trp Ala Gln His Val Gly Ala Glu Val His Ala Thr Ala
1105 1110 1115 1120

Gly Thr Pro Glu Lys Arg Ala Tyr Leu Glu Ser Leu Gly Val Arg Tyr
1125 1130 1135

Val Ser Asp Ser Arg Ser Asp Arg Phe Val Ala Asp Val Arg Ala Trp
1140 1145 1150

Thr Gly Gly Glu Gly Val Asp Val Val Leu Asn Ser Leu Ser Gly Glu
1155 1160 1165

Leu Ile Asp Lys Ser Phe Asn Leu Leu Arg Ser His Gly Arg Phe Val
1170 1175 1180

Glu Leu Gly Lys Arg Asp Cys Tyr Ala Asp Asn Gln Leu Gly Leu Arg
1185 1190 1195 1200

Pro Phe Leu Arg Asn Leu Ser Phe Ser Leu Val Asp Leu Arg Gly Met
1205 1210 1215

Met Leu Glu Arg Pro Ala Arg Val Arg Ala Leu Leu Glu Glu Leu Leu
1220 1225 1230

Gly Leu Ile Ala Ala Gly Val Phe Thr Pro Pro Pro Ile Ala Thr Leu
1235 1240 1245

Pro Ile Ala Arg Val Ala Asp Ala Phe Arg Ser Met Ala Gln Ala Gln
1250 1255 1260

His Leu Gly Lys Leu Val Leu Thr Leu Gly Asp Pro Glu Val Gln Ile
1265 1270 1275 1280

Arg Ile Pro Thr His Ala Gly Ala Gly Pro Ser Thr Gly Asp Arg Asp
1285 1290 1295

Leu Leu Asp Arg Leu Ala Ser Ala Ala Pro Ala Ala Arg Ala Ala Ala
1300 1305 1310

Leu Glu Ala Phe Leu Arg Thr Gln Val Ser Gln Val Leu Arg Thr Pro
1315 1320 1325

Glu Ile Lys Val Gly Ala Glu Ala Leu Phe Thr Arg Leu Gly Met Asp
1330 1335 1340

Ser Leu Met Ala Val Glu Leu Arg Asn Arg Ile Glu Ala Ser Leu Lys
1345 1350 1355 1360

Leu Lys Leu Ser Thr Thr Phe Leu Ser Thr Ser Pro Asn Ile Ala Leu

1365 1370 1375

Leu Ala Gln Asn Leu Leu Asp Ala Leu Ala Thr Ala Leu Ser Leu Glu
1380 1385 1390

Arg Val Ala Ala Glu Asn Leu Arg Ala Gly Val Gln Asn Asp Phe Val
1395 1400 1405

Ser Ser Gly Ala Asp Gln Asp Trp Glu Ile Ile Ala Leu
1410 1415 1420

<210> 3
<211> 1410
<212> PRT
<213> Sorangium cellulosum

<400> 3
Met Thr Ile Asn Gln Leu Leu Asn Glu Leu Glu His Gln Gly Ile Lys
1 5 10 15

Leu Ala Ala Asp Gly Glu Arg Leu Gln Ile Gln Ala Pro Lys Asn Ala
20 25 30

Leu Asn Pro Asn Leu Leu Ala Arg Ile Ser Glu His Lys Ser Thr Ile
35 40 45

Leu Thr Met Leu Arg Gln Arg Leu Pro Ala Glu Ser Ile Val Pro Ala
50 55 60

Pro Ala Glu Arg His Ala Pro Phe Pro Leu Thr Asp Ile Gln Glu Ser
65 70 75 80

Tyr Trp Leu Gly Arg Thr Gly Ala Phe Thr Val Pro Ser Gly Ile His
85 90 95

Ala Tyr Arg Glu Tyr Asp Cys Thr Asp Leu Asp Val Pro Arg Leu Ser
100 105 110

Arg Ala Phe Arg Lys Val Val Ala Arg His Asp Met Leu Arg Ala His
115 120 125

Thr Leu Pro Asp Met Met Gln Val Ile Glu Pro Lys Val Asp Ala Asp
130 135 140

Ile Glu Ile Ile Asp Leu Arg Gly Leu Asp Arg Ser Thr Arg Glu Ala
145 150 155 160

Arg Leu Val Ser Leu Arg Asp Ala Met Ser His Arg Ile Tyr Asp Thr
165 170 175

Glu Arg Pro Pro Leu Tyr His Val Val Ala Val Arg Leu Asp Glu Arg
180 185 190

Gln Thr Arg Leu Val Leu Ser Ile Asp Leu Ile Asn Val Asp Leu Gly
195 200 205

Ser Leu Ser Ile Ile Phe Lys Asp Trp Leu Ser Phe Tyr Glu Asp Pro
210 215 220

Glu Thr Ser Leu Pro Val Leu Glu Leu Ser Tyr Arg Asp Tyr Val Leu
225 230 235 240

Ala Leu Glu Ser Arg Lys Lys Ser Glu Ala His Gln Arg Ser Met Asp
245 250 255

```
Tyr Trp Lys Arg Arg Ile Ala Glu Leu Pro Pro Pro Pro Thr Leu Pro
            260                 265                 270

Met Lys Ala Asp Pro Ser Thr Leu Lys Glu Ile Arg Phe Arg His Thr
        275                 280                 285

Glu Gln Trp Leu Pro Ser Asp Ser Trp Gly Arg Leu Lys Arg Arg Val
    290                 295                 300

Gly Glu Arg Gly Leu Thr Pro Thr Gly Val Ile Leu Ala Ala Phe Ser
305                 310                 315                 320

Glu Val Ile Gly Arg Trp Ser Ala Ser Pro Arg Phe Thr Leu Asn Ile
                325                 330                 335

Thr Leu Phe Asn Arg Leu Pro Val His Pro Arg Val Asn Asp Ile Thr
            340                 345                 350

Gly Asp Phe Thr Ser Met Val Leu Leu Asp Ile Asp Thr Thr Arg Asp
        355                 360                 365

Lys Ser Phe Glu Gln Arg Ala Lys Arg Ile Gln Glu Gln Leu Trp Glu
    370                 375                 380

Ala Met Asp His Cys Asp Val Ser Gly Ile Glu Val Gln Arg Glu Ala
385                 390                 395                 400

Ala Arg Val Leu Gly Ile Gln Arg Gly Ala Leu Phe Pro Val Val Leu
                405                 410                 415

Thr Ser Ala Leu Asn Gln Gln Val Val Gly Val Thr Ser Leu Gln Arg
            420                 425                 430

Leu Gly Thr Pro Val Tyr Thr Ser Thr Gln Thr Pro Gln Leu Leu Leu
        435                 440                 445

Asp His Gln Leu Tyr Glu His Asp Gly Asp Leu Val Leu Ala Trp Asp
    450                 455                 460

Ile Val Asp Gly Val Phe Pro Pro Asp Leu Leu Asp Asp Met Leu Glu
465                 470                 475                 480

Ala Tyr Val Val Phe Leu Arg Arg Leu Thr Glu Glu Pro Trp Gly Glu
                485                 490                 495

Gln Val Arg Cys Ser Leu Pro Pro Ala Gln Leu Glu Ala Arg Ala Ser
            500                 505                 510

Ala Asn Ala Thr Asn Ala Leu Leu Ser Glu His Thr Leu His Gly Leu
        515                 520                 525

Phe Ala Ala Arg Val Glu Gln Leu Pro Met Gln Leu Ala Val Val Ser
    530                 535                 540

Ala Arg Lys Thr Leu Thr Tyr Glu Glu Leu Ser Arg Arg Ser Arg Arg
545                 550                 555                 560

Leu Gly Ala Arg Leu Arg Glu Gln Gly Ala Arg Pro Asn Thr Leu Val
                565                 570                 575

Ala Val Val Met Glu Lys Gly Trp Glu Gln Val Val Ala Val Leu Ala
            580                 585                 590

Val Leu Glu Ser Gly Ala Ala Tyr Val Pro Ile Asp Ala Asp Leu Pro
```

```
        595                 600                 605

Ala Glu Arg Ile His Tyr Leu Leu Asp His Gly Glu Val Lys Leu Val
    610                 615                 620

Leu Thr Gln Pro Trp Leu Asp Gly Lys Leu Ser Trp Pro Pro Gly Ile
625                 630                 635                 640

Gln Arg Leu Leu Val Ser Glu Ala Gly Val Glu Gly Asp Gly Asp Gln
                645                 650                 655

Pro Pro Met Met Pro Ile Gln Thr Pro Ser Asp Leu Ala Tyr Val Ile
            660                 665                 670

Tyr Thr Ser Gly Ser Thr Gly Leu Pro Lys Gly Val Met Ile Asp His
        675                 680                 685

Arg Gly Ala Val Asn Thr Ile Leu Asp Ile Asn Glu Arg Phe Glu Ile
    690                 695                 700

Gly Pro Gly Asp Arg Val Leu Ala Leu Ser Ser Leu Ser Phe Asp Leu
705                 710                 715                 720

Ser Val Tyr Asp Val Phe Gly Ile Leu Ala Ala Gly Gly Thr Ile Val
                725                 730                 735

Val Pro Asp Ala Ser Lys Leu Arg Asp Pro Ala His Trp Ala Glu Leu
            740                 745                 750

Ile Glu Arg Glu Lys Val Thr Val Trp Asn Ser Val Pro Ala Leu Met
        755                 760                 765

Arg Met Leu Val Glu His Phe Glu Gly Arg Pro Asp Ser Leu Ala Arg
    770                 775                 780

Ser Leu Arg Leu Ser Leu Leu Ser Gly Asp Trp Ile Pro Val Gly Leu
785                 790                 795                 800

Pro Gly Glu Leu Gln Ala Ile Arg Pro Gly Val Ser Val Ile Ser Leu
                805                 810                 815

Gly Gly Ala Thr Glu Ala Ser Ile Trp Ser Ile Gly Tyr Pro Val Arg
            820                 825                 830

Asn Val Asp Leu Ser Trp Ala Ser Ile Pro Tyr Gly Arg Pro Leu Arg
        835                 840                 845

Asn Gln Thr Phe His Val Leu Asp Glu Ala Leu Glu Pro Arg Pro Val
    850                 855                 860

Trp Val Pro Gly Gln Leu Tyr Ile Gly Gly Val Gly Leu Ala Leu Gly
865                 870                 875                 880

Tyr Trp Arg Asp Glu Glu Lys Thr Arg Lys Ser Phe Leu Val His Pro
                885                 890                 895

Glu Thr Gly Glu Arg Leu Tyr Lys Thr Gly Asp Leu Gly Arg Tyr Leu
            900                 905                 910

Pro Asp Gly Asn Ile Glu Phe Met Gly Arg Glu Asp Asn Gln Ile Lys
        915                 920                 925

Leu Arg Gly Tyr Arg Val Glu Leu Gly Glu Ile Glu Glu Thr Leu Lys
    930                 935                 940
```

Ser His Pro Asn Val Arg Asp Ala Val Ile Val Pro Val Gly Asn Asp
945 950 955 960

Ala Ala Asn Lys Leu Leu Leu Ala Tyr Val Val Pro Glu Gly Thr Arg
965 970 975

Arg Arg Ala Ala Glu Gln Asp Ala Ser Leu Lys Thr Glu Arg Ile Asp
980 985 990

Ala Arg Ala His Ala Ala Glu Ala Asp Gly Leu Ser Asp Gly Glu Arg
995 1000 1005

Val Gln Phe Lys Leu Ala Arg His Gly Leu Arg Arg Asp Leu Asp Gly
1010 1015 1020

Lys Pro Val Val Asp Leu Thr Gly Gln Asp Pro Arg Glu Ala Gly Leu
1025 1030 1035 1040

Asp Val Tyr Ala Arg Arg Arg Ser Val Arg Thr Phe Leu Glu Ala Pro
1045 1050 1055

Ile Pro Phe Val Glu Phe Gly Arg Phe Leu Ser Cys Leu Ser Ser Val
1060 1065 1070

Glu Pro Asp Gly Ala Thr Leu Pro Lys Phe Arg Tyr Pro Ser Ala Gly
1075 1080 1085

Ser Thr Tyr Pro Val Gln Thr Tyr Ala Tyr Val Lys Ser Gly Arg Ile
1090 1095 1100

Glu Gly Val Asp Glu Gly Phe Tyr Tyr Tyr His Pro Phe Glu His Arg
1105 1110 1115 1120

Leu Leu Lys Leu Ser Asp His Gly Ile Glu Arg Gly Ala His Val Arg
1125 1130 1135

Gln Asn Phe Asp Val Phe Asp Glu Ala Ala Phe Asn Leu Leu Phe Val
1140 1145 1150

Gly Arg Ile Asp Ala Ile Glu Ser Leu Tyr Gly Ser Ser Ser Arg Glu
1155 1160 1165

Phe Cys Leu Leu Glu Ala Gly Tyr Met Ala Gln Leu Leu Met Glu Gln
1170 1175 1180

Ala Pro Ser Cys Asn Ile Gly Val Cys Pro Val Gly Gln Phe Asn Phe
1185 1190 1195 1200

Glu Gln Val Arg Pro Val Leu Asp Leu Arg His Ser Asp Val Tyr Val
1205 1210 1215

His Gly Met Leu Gly Gly Arg Val Asp Pro Arg Gln Phe Gln Val Cys
1220 1225 1230

Thr Leu Gly Gln Asp Ser Ser Pro Arg Arg Ala Thr Thr Arg Gly Ala
1235 1240 1245

Pro Pro Gly Arg Glu Gln His Phe Ala Asp Met Leu Arg Asp Phe Leu
1250 1255 1260

Arg Thr Lys Leu Pro Glu Tyr Met Val Pro Thr Val Phe Val Glu Leu
1265 1270 1275 1280

Asp Ala Leu Pro Leu Thr Ser Asn Gly Lys Val Asp Arg Lys Ala Leu
1285 1290 1295

Arg Glu Arg Lys Asp Thr Ser Ser Pro Arg His Ser Gly His Thr Ala
1300 1305 1310

Pro Arg Asp Ala Leu Glu Glu Ile Leu Val Ala Val Val Arg Glu Val
1315 1320 1325

Leu Gly Leu Glu Val Val Gly Leu Gln Gln Ser Phe Val Asp Leu Gly
1330 1335 1340

Ala Thr Ser Ile His Ile Val Arg Met Arg Ser Leu Leu Gln Lys Arg
1345 1350 1355 1360

Leu Asp Arg Glu Ile Ala Ile Thr Glu Leu Phe Gln Tyr Pro Asn Leu
1365 1370 1375

Gly Ser Leu Ala Ser Gly Leu Arg Arg Asp Ser Arg Asp Leu Asp Gln
1380 1385 1390

Arg Pro Asn Met Gln Asp Arg Val Glu Val Arg Arg Lys Gly Arg Arg
1395 1400 1405

Arg Ser
1410

<210> 4
<211> 1832
<212> PRT
<213> Sorangium cellulosum

<400> 4
Met Glu Glu Gln Glu Ser Ser Ala Ile Ala Val Ile Gly Met Ser Gly
1 5 10 15

Arg Phe Pro Gly Ala Arg Asp Leu Asp Glu Phe Trp Arg Asn Leu Arg
20 25 30

Asp Gly Thr Glu Ala Val Gln Arg Phe Ser Glu Gln Glu Leu Ala Ala
35 40 45

Ser Gly Val Asp Pro Ala Leu Val Leu Asp Pro Ser Tyr Val Arg Ala
50 55 60

Gly Ser Val Leu Glu Asp Val Asp Arg Phe Asp Ala Ala Phe Phe Gly
65 70 75 80

Ile Ser Pro Arg Glu Ala Glu Leu Met Asp Pro Gln His Arg Ile Phe
85 90 95

Met Glu Cys Ala Trp Glu Ala Leu Glu Asn Ala Gly Tyr Asp Pro Thr
100 105 110

Ala Tyr Glu Gly Ser Ile Gly Val Tyr Ala Gly Ala Asn Met Ser Ser
115 120 125

Tyr Leu Thr Ser Asn Leu His Glu His Pro Ala Met Met Arg Trp Pro
130 135 140

Gly Trp Phe Gln Thr Leu Ile Gly Asn Asp Lys Asp Tyr Leu Ala Thr
145 150 155 160

His Val Ser Tyr Arg Leu Asn Leu Arg Gly Pro Ser Ile Ser Val Gln
165 170 175

Thr Ala Cys Ser Thr Ser Leu Val Ala Val His Leu Ala Cys Met Ser
180 185 190

Leu Leu Asp Arg Glu Cys Asp Met Ala Leu Ala Gly Gly Ile Thr Val
195 200 205

Arg Ile Pro His Arg Ala Gly Tyr Val Tyr Ala Glu Gly Gly Ile Phe
210 215 220

Ser Pro Asp Gly His Cys Arg Ala Phe Asp Ala Lys Ala Asn Gly Thr
225 230 235 240

Ile Met Gly Asn Gly Cys Gly Val Val Leu Leu Lys Pro Leu Asp Arg
245 250 255

Ala Leu Ser Asp Gly Asp Pro Val Arg Ala Val Ile Leu Gly Ser Ala
260 265 270

Thr Asn Asn Asp Gly Ala Arg Lys Ile Gly Phe Thr Ala Pro Ser Glu
275 280 285

Val Gly Gln Ala Gln Ala Ile Met Glu Ala Leu Ala Leu Ala Gly Val
290 295 300

Glu Ala Arg Ser Ile Gln Tyr Ile Glu Thr His Gly Thr Gly Thr Leu
305 310 315 320

Leu Gly Asp Ala Ile Glu Thr Ala Ala Leu Arg Arg Val Phe Gly Arg
325 330 335

Asp Ala Ser Ala Arg Arg Ser Cys Ala Ile Gly Ser Val Lys Thr Gly
340 345 350

Ile Gly His Leu Glu Ser Ala Ala Gly Ile Ala Gly Leu Ile Lys Thr
355 360 365

Val Leu Ala Leu Glu His Arg Gln Leu Pro Pro Ser Leu Asn Phe Glu
370 375 380

Ser Pro Asn Pro Ser Ile Asp Phe Ala Ser Ser Pro Phe Tyr Val Asn
385 390 395 400

Thr Ser Leu Lys Asp Trp Asn Thr Gly Ser Thr Pro Arg Arg Ala Gly
405 410 415

Val Ser Ser Phe Gly Ile Gly Gly Thr Asn Ala His Val Val Leu Glu
420 425 430

Glu Ala Pro Ala Ala Lys Leu Pro Ala Ala Ala Pro Ala Arg Ser Ala
435 440 445

Glu Leu Phe Val Val Ser Ala Lys Ser Ala Ala Ala Leu Asp Ala Ala
450 455 460

Ala Ala Arg Leu Arg Asp His Leu Gln Ala His Gln Gly Ile Ser Leu
465 470 475 480

Gly Asp Val Ala Phe Ser Leu Ala Thr Thr Arg Ser Pro Met Glu His
485 490 495

Arg Leu Ala Met Ala Ala Pro Ser Arg Glu Ala Leu Arg Glu Gly Leu
500 505 510

Asp Ala Ala Ala Arg Gly Gln Thr Pro Pro Gly Ala Val Arg Gly Arg
515 520 525

Cys Ser Pro Gly Asn Val Pro Lys Val Val Phe Val Phe Pro Gly Gln
530 535 540

Gly Ser Gln Trp Val Gly Met Gly Arg Gln Leu Leu Ala Glu Glu Pro
545 550 555 560

Val Phe His Ala Ala Leu Ser Ala Cys Asp Arg Ala Ile Gln Ala Glu
565 570 575

Ala Gly Trp Ser Leu Leu Ala Glu Leu Ala Ala Asp Glu Gly Ser Ser
580 585 590

Gln Leu Glu Arg Ile Asp Val Val Gln Pro Val Leu Phe Ala Leu Ala
595 600 605

Val Ala Phe Ala Ala Leu Trp Arg Ser Trp Gly Val Ala Pro Asp Val
610 615 620

Val Ile Gly His Ser Met Gly Glu Val Ala Ala Ala His Val Ala Gly
625 630 635 640

Ala Leu Ser Leu Glu Asp Ala Val Ala Ile Ile Cys Arg Arg Ser Arg
645 650 655

Leu Leu Arg Arg Ile Ser Gly Gln Gly Glu Met Ala Val Thr Glu Leu
660 665 670

Ser Leu Ala Glu Ala Glu Ala Ala Leu Arg Gly Tyr Glu Asp Arg Val
675 680 685

Ser Val Ala Val Ser Asn Ser Pro Arg Ser Thr Val Leu Ser Gly Glu
690 695 700

Pro Ala Ala Ile Gly Glu Val Leu Ser Ser Leu Asn Ala Lys Gly Val
705 710 715 720

Phe Cys Arg Arg Val Lys Val Asp Val Ala Ser His Ser Pro Gln Val
725 730 735

Asp Pro Leu Arg Glu Asp Leu Leu Ala Ala Leu Gly Gly Leu Arg Pro
740 745 750

Gly Ala Ala Ala Val Pro Met Arg Ser Thr Val Thr Gly Ala Met Val
755 760 765

Ala Gly Pro Glu Leu Gly Ala Asn Tyr Trp Met Asn Asn Leu Arg Gln
770 775 780

Pro Val Arg Phe Ala Glu Val Val Gln Ala Gln Leu Gln Gly Gly His
785 790 795 800

Gly Leu Phe Val Glu Met Ser Pro His Pro Ile Leu Thr Thr Ser Val
805 810 815

Glu Glu Met Arg Arg Ala Ala Gln Arg Ala Gly Ala Ala Val Gly Ser
820 825 830

Leu Arg Arg Gly Gln Asp Glu Arg Pro Ala Met Leu Glu Ala Leu Gly
835 840 845

Thr Leu Trp Ala Gln Gly Tyr Pro Val Pro Trp Gly Arg Leu Phe Pro
850 855 860

Ala Gly Gly Arg Arg Val Pro Leu Pro Thr Tyr Pro Trp Gln Arg Glu

865 870 875 880

Arg Tyr Trp Ile Glu Ala Pro Ala Lys Ser Ala Ala Gly Asp Arg Arg
885 890 895

Gly Val Arg Ala Gly Gly His Pro Leu Leu Gly Glu Met Gln Thr Leu
900 905 910

Ser Thr Gln Thr Ser Thr Arg Leu Trp Glu Thr Thr Leu Asp Leu Lys
915 920 925

Arg Leu Pro Trp Leu Gly Asp His Arg Val Gln Gly Ala Val Val Phe
930 935 940

Pro Gly Ala Ala Tyr Leu Glu Met Ala Ile Ser Ser Gly Ala Glu Ala
945 950 955 960

Leu Gly Asp Gly Pro Leu Gln Ile Thr Asp Val Val Leu Ala Glu Ala
965 970 975

Leu Ala Phe Ala Gly Asp Ala Ala Val Leu Val Gln Val Val Thr Thr
980 985 990

Glu Gln Pro Ser Gly Arg Leu Gln Phe Gln Ile Ala Ser Arg Ala Pro
995 1000 1005

Gly Ala Gly His Ala Ser Phe Arg Val His Ala Arg Gly Ala Leu Leu
1010 1015 1020

Arg Val Glu Arg Thr Glu Val Pro Ala Gly Leu Thr Leu Ser Ala Val
1025 1030 1035 1040

Arg Ala Arg Leu Gln Ala Ser Ile Pro Ala Ala Ala Thr Tyr Ala Glu
1045 1050 1055

Leu Thr Glu Met Gly Leu Gln Tyr Gly Pro Ala Phe Gln Gly Ile Ala
1060 1065 1070

Glu Leu Trp Arg Gly Glu Gly Glu Ala Leu Gly Arg Val Arg Leu Pro
1075 1080 1085

Asp Ala Ala Gly Ser Ala Ala Glu Tyr Arg Leu His Pro Ala Leu Leu
1090 1095 1100

Asp Ala Cys Phe Gln Ile Val Gly Ser Leu Phe Ala Arg Ser Gly Glu
1105 1110 1115 1120

Ala Thr Pro Trp Val Pro Val Glu Leu Gly Ser Leu Arg Leu Leu Gln
1125 1130 1135

Arg Pro Ser Gly Glu Leu Trp Cys His Ala Arg Val Val Asn His Gly
1140 1145 1150

His Gln Thr Pro Asp Arg Gln Gly Ala Asp Phe Trp Val Val Asp Ser
1155 1160 1165

Ser Gly Ala Val Val Ala Glu Val Cys Gly Leu Val Ala Gln Arg Leu
1170 1175 1180

Pro Gly Gly Val Arg Arg Arg Glu Glu Asp Asp Trp Phe Leu Glu Leu
1185 1190 1195 1200

Glu Trp Glu Pro Ala Ala Val Gly Thr Ala Lys Val Asn Ala Gly Arg
1205 1210 1215

```
Trp Leu Leu Leu Gly Gly Gly Gly Gly Leu Gly Ala Ala Leu Arg Ala
            1220                1225                1230

Met Leu Glu Ala Gly Gly His Ala Val Val His Ala Ala Glu Asn Asn
        1235                1240                1245

Thr Ser Ala Ala Gly Val Arg Ala Leu Leu Ala Lys Ala Phe Asp Gly
    1250                1255                1260

Gln Ala Pro Thr Ala Val Val His Leu Gly Ser Leu Asp Gly Gly Gly
1265                1270                1275                1280

Glu Leu Asp Pro Gly Leu Gly Ala Gln Gly Ala Leu Asp Ala Pro Arg
                1285                1290                1295

Ser Ala Asp Val Ser Pro Asp Ala Leu Asp Pro Ala Leu Val Arg Gly
            1300                1305                1310

Cys Asp Ser Val Leu Trp Thr Val Gln Ala Leu Ala Gly Met Gly Phe
        1315                1320                1325

Arg Asp Ala Pro Arg Leu Trp Leu Leu Thr Arg Gly Ala Gln Ala Val
    1330                1335                1340

Gly Ala Gly Asp Val Ser Val Thr Gln Ala Pro Leu Leu Gly Leu Gly
1345                1350                1355                1360

Arg Val Ile Ala Met Glu His Ala Asp Leu Arg Cys Ala Arg Val Asp
                1365                1370                1375

Leu Asp Pro Ala Arg Pro Glu Gly Glu Leu Ala Ala Leu Leu Ala Glu
            1380                1385                1390

Leu Leu Ala Asp Asp Ala Glu Ala Glu Val Ala Leu Arg Gly Gly Glu
        1395                1400                1405

Arg Cys Val Ala Arg Ile Val Arg Arg Gln Pro Glu Thr Arg Pro Arg
    1410                1415                1420

Gly Arg Ile Glu Ser Cys Val Pro Thr Asp Val Thr Ile Arg Ala Asp
1425                1430                1435                1440

Ser Thr Tyr Leu Val Thr Gly Gly Leu Gly Gly Leu Gly Leu Ser Val
                1445                1450                1455

Ala Gly Trp Leu Ala Glu Arg Gly Ala Gly His Leu Val Leu Val Gly
            1460                1465                1470

Arg Ser Gly Ala Ala Ser Val Glu Gln Arg Ala Ala Val Ala Ala Leu
        1475                1480                1485

Glu Ala Arg Gly Ala Arg Val Thr Val Ala Lys Ala Asp Val Ala Asp
    1490                1495                1500

Arg Ala Gln Leu Glu Arg Ile Leu Arg Glu Val Thr Thr Ser Gly Met
1505                1510                1515                1520

Pro Leu Arg Gly Val Val His Ala Ala Gly Ile Leu Asp Asp Gly Leu
                1525                1530                1535

Leu Met Gln Gln Thr Pro Ala Arg Phe Arg Lys Val Met Ala Pro Lys
            1540                1545                1550

Val Gln Gly Ala Leu His Leu His Ala Leu Thr Arg Glu Ala Pro Leu
        1555                1560                1565
```

Ser Phe Phe Val Leu Tyr Ala Ser Gly Val Gly Leu Leu Gly Ser Pro
1570 1575 1580

Gly Gln Gly Asn Tyr Ala Ala Ala Asn Thr Phe Leu Asp Ala Leu Ala
1585 1590 1595 1600

His His Arg Arg Ala Gln Gly Leu Pro Ala Leu Ser Val Asp Trp Gly
1605 1610 1615

Leu Phe Ala Glu Val Gly Met Ala Ala Ala Gln Glu Asp Arg Gly Ala
1620 1625 1630

Arg Leu Val Ser Arg Gly Met Arg Ser Leu Thr Pro Asp Glu Gly Leu
1635 1640 1645

Ser Ala Leu Ala Arg Leu Leu Glu Ser Gly Arg Ala Gln Val Gly Val
1650 1655 1660

Met Pro Val Asn Pro Arg Leu Trp Val Glu Leu Tyr Pro Ala Ala Ala
1665 1670 1675 1680

Ser Ser Arg Met Leu Ser Arg Leu Val Thr Ala His Arg Ala Ser Ala
1685 1690 1695

Gly Gly Pro Ala Gly Asp Gly Asp Leu Leu Arg Arg Leu Ala Ala Ala
1700 1705 1710

Glu Pro Ser Ala Arg Ser Ala Leu Leu Glu Pro Leu Leu Arg Ala Gln
1715 1720 1725

Ile Ser Gln Val Leu Arg Leu Pro Glu Gly Lys Ile Glu Val Asp Ala
1730 1735 1740

Pro Leu Thr Ser Leu Gly Met Asn Ser Leu Met Gly Leu Glu Leu Arg
1745 1750 1755 1760

Asn Arg Ile Glu Ala Met Leu Gly Ile Thr Val Pro Ala Thr Leu Leu
1765 1770 1775

Trp Thr Tyr Pro Thr Val Ala Ala Leu Ser Gly His Leu Ala Arg Glu
1780 1785 1790

Ala Cys Glu Ala Ala Pro Val Glu Ser Pro His Thr Thr Ala Asp Ser
1795 1800 1805

Ala Val Glu Ile Glu Glu Met Ser Gln Asp Asp Leu Thr Gln Leu Ile
1810 1815 1820

Ala Ala Lys Phe Lys Ala Leu Thr
1825 1830

<210> 5
<211> 7257
<212> PRT
<213> Sorangium cellulosum

<400> 5
Met Thr Thr Arg Gly Pro Thr Ala Gln Gln Asn Pro Leu Lys Gln Ala
1 5 10 15

Ala Ile Ile Ile Gln Arg Leu Glu Glu Arg Leu Ala Gly Leu Ala Gln
20 25 30

```
Ala Glu Leu Glu Arg Thr Glu Pro Ile Ala Ile Val Gly Ile Gly Cys
        35                  40                  45

Arg Phe Pro Gly Gly Ala Asp Ala Pro Glu Ala Phe Trp Glu Leu Leu
    50                  55                  60

Asp Ala Glu Arg Asp Ala Val Gln Pro Leu Asp Met Arg Trp Ala Leu
65                  70                  75                  80

Val Gly Val Ala Pro Val Glu Ala Val Pro His Trp Ala Gly Leu Leu
                85                  90                  95

Thr Glu Pro Ile Asp Cys Phe Asp Ala Ala Phe Phe Gly Ile Ser Pro
            100                 105                 110

Arg Glu Ala Arg Ser Leu Asp Pro Gln His Arg Leu Leu Leu Glu Val
        115                 120                 125

Ala Trp Glu Gly Leu Glu Asp Ala Gly Ile Pro Pro Arg Ser Ile Asp
    130                 135                 140

Gly Ser Arg Thr Gly Val Phe Val Gly Ala Phe Thr Ala Asp Tyr Ala
145                 150                 155                 160

Arg Thr Val Ala Arg Leu Pro Arg Glu Glu Arg Asp Ala Tyr Ser Ala
                165                 170                 175

Thr Gly Asn Met Leu Ser Ile Ala Ala Gly Arg Leu Ser Tyr Thr Leu
            180                 185                 190

Gly Leu Gln Gly Pro Cys Leu Thr Val Asp Thr Ala Cys Ser Ser Ser
        195                 200                 205

Leu Val Ala Ile His Leu Ala Cys Arg Ser Leu Arg Ala Gly Glu Ser
    210                 215                 220

Asp Leu Ala Leu Ala Gly Gly Val Ser Ala Leu Leu Ser Pro Asp Met
225                 230                 235                 240

Met Glu Ala Ala Ala Arg Thr Gln Ala Leu Ser Pro Asp Gly Arg Cys
                245                 250                 255

Arg Thr Phe Asp Ala Ser Ala Asn Gly Phe Val Arg Gly Glu Gly Cys
            260                 265                 270

Gly Leu Val Val Leu Lys Arg Leu Ser Asp Ala Gln Arg Asp Gly Asp
        275                 280                 285

Arg Ile Trp Ala Leu Ile Arg Gly Ser Ala Ile Asn His Asp Gly Arg
    290                 295                 300

Ser Thr Gly Leu Thr Ala Pro Asn Val Leu Ala Gln Glu Thr Val Leu
305                 310                 315                 320

Arg Glu Ala Leu Arg Ser Ala His Val Glu Ala Gly Ala Val Asp Tyr
                325                 330                 335

Val Glu Thr His Gly Thr Gly Thr Ser Leu Gly Asp Pro Ile Glu Val
            340                 345                 350

Glu Ala Leu Arg Ala Thr Val Gly Pro Ala Arg Ser Asp Gly Thr Arg
        355                 360                 365

Cys Val Leu Gly Ala Val Lys Thr Asn Ile Gly His Leu Glu Ala Ala
    370                 375                 380
```

Ala Gly Val Ala Gly Leu Ile Lys Ala Ala Leu Ser Leu Thr His Glu
385 390 395 400

Arg Ile Pro Arg Asn Leu Asn Phe Arg Thr Leu Asn Pro Arg Ile Arg
405 410 415

Leu Glu Gly Ser Ala Leu Ala Leu Ala Thr Glu Pro Val Pro Trp Pro
420 425 430

Arg Thr Asp Arg Pro Arg Phe Ala Gly Val Ser Ser Phe Gly Met Ser
435 440 445

Gly Thr Asn Ala His Val Val Leu Glu Glu Ala Pro Ala Val Glu Leu
450 455 460

Trp Pro Ala Ala Pro Glu Arg Ser Ala Glu Leu Leu Val Leu Ser Gly
465 470 475 480

Lys Ser Glu Gly Ala Leu Asp Ala Gln Ala Ala Arg Leu Arg Glu His
485 490 495

Leu Asp Met His Pro Glu Leu Gly Leu Gly Asp Val Ala Phe Ser Leu
500 505 510

Ala Thr Thr Arg Ser Ala Met Ser His Arg Leu Ala Val Ala Val Thr
515 520 525

Ser Arg Glu Gly Leu Leu Ala Ala Leu Ser Ala Val Ala Gln Gly Gln
530 535 540

Thr Pro Ala Gly Ala Ala Arg Cys Ile Ala Ser Ser Ser Arg Gly Lys
545 550 555 560

Leu Ala Phe Leu Phe Thr Gly Gln Gly Ala Gln Thr Pro Gly Met Gly
565 570 575

Arg Gly Leu Cys Ala Ala Trp Pro Ala Phe Arg Glu Ala Phe Asp Arg
580 585 590

Cys Val Ala Leu Phe Asp Arg Glu Leu Asp Arg Pro Leu Arg Glu Val
595 600 605

Met Trp Ala Glu Ala Gly Ser Ala Glu Ser Leu Leu Leu Asp Gln Thr
610 615 620

Ala Phe Thr Gln Pro Ala Leu Phe Ala Val Glu Tyr Ala Leu Thr Ala
625 630 635 640

Leu Trp Arg Ser Trp Gly Val Glu Pro Glu Leu Leu Val Gly His Ser
645 650 655

Ile Gly Glu Leu Val Ala Ala Cys Val Ala Gly Val Phe Ser Leu Glu
660 665 670

Asp Gly Val Arg Leu Val Ala Ala Arg Gly Arg Leu Met Gln Gly Leu
675 680 685

Ser Ala Gly Gly Ala Met Val Ser Leu Gly Ala Pro Glu Ala Glu Val
690 695 700

Ala Ala Ala Val Ala Pro His Ala Ala Ser Val Ser Ile Ala Ala Val
705 710 715 720

Asn Gly Pro Glu Gln Val Val Ile Ala Gly Val Glu Gln Ala Val Gln

725 730 735

Ala Ile Ala Ala Gly Phe Ala Ala Arg Gly Ala Arg Thr Lys Arg Leu
740 745 750

His Val Ser His Ala Phe His Ser Pro Leu Met Glu Pro Met Leu Glu
755 760 765

Glu Phe Gly Arg Val Ala Ala Ser Val Thr Tyr Arg Arg Pro Ser Val
770 775 780

Ser Leu Val Ser Asn Leu Ser Gly Lys Val Val Thr Asp Glu Leu Ser
785 790 795 800

Ala Pro Gly Tyr Trp Val Arg His Val Arg Glu Ala Val Arg Phe Ala
805 810 815

Asp Gly Val Lys Ala Leu His Glu Ala Gly Ala Gly Thr Phe Val Glu
820 825 830

Val Gly Pro Lys Pro Thr Leu Leu Gly Leu Leu Pro Ala Cys Leu Pro
835 840 845

Glu Ala Glu Pro Thr Leu Leu Ala Ser Leu Arg Ala Gly Arg Glu Glu
850 855 860

Ala Ala Gly Val Leu Glu Ala Leu Gly Arg Leu Trp Ala Ala Gly Gly
865 870 875 880

Ser Val Ser Trp Pro Gly Val Phe Pro Thr Ala Gly Arg Arg Val Pro
885 890 895

Leu Pro Thr Tyr Pro Trp Gln Arg Gln Arg Tyr Trp Ile Glu Ala Pro
900 905 910

Ala Glu Gly Leu Gly Ala Thr Ala Ala Asp Ala Leu Ala Gln Trp Phe
915 920 925

Tyr Arg Val Asp Trp Pro Glu Met Pro Arg Ser Ser Val Asp Ser Arg
930 935 940

Arg Ala Arg Ser Gly Gly Trp Leu Val Leu Ala Asp Arg Gly Gly Val
945 950 955 960

Gly Glu Ala Ala Ala Ala Ala Leu Ser Ser Gln Gly Cys Ser Cys Ala
965 970 975

Val Leu His Ala Pro Ala Glu Ala Ser Ala Val Ala Glu Gln Val Thr
980 985 990

Gln Ala Leu Gly Gly Arg Asn Asp Trp Gln Gly Val Leu Tyr Leu Trp
995 1000 1005

Gly Leu Asp Ala Val Val Glu Ala Gly Ala Ser Ala Glu Glu Val Ala
1010 1015 1020

Lys Val Thr His Leu Ala Ala Ala Pro Val Leu Ala Leu Ile Gln Ala
1025 1030 1035 1040

Leu Gly Thr Gly Pro Arg Ser Pro Arg Leu Trp Ile Val Thr Arg Gly
1045 1050 1055

Ala Cys Thr Val Gly Gly Glu Pro Asp Ala Ala Pro Cys Gln Ala Ala
1060 1065 1070

Leu Trp Gly Met Gly Arg Val Ala Ala Leu Glu His Pro Gly Ser Trp
1075 1080 1085

Gly Gly Leu Val Asp Leu Asp Pro Glu Glu Ser Pro Thr Glu Val Glu
1090 1095 1100

Ala Leu Val Ala Glu Leu Leu Ser Pro Asp Ala Glu Asp Gln Leu Ala
1105 1110 1115 1120

Phe Arg Gln Gly Arg Arg Arg Ala Ala Arg Leu Val Ala Ala Pro Pro
1125 1130 1135

Glu Gly Asn Ala Ala Pro Val Ser Leu Ser Ala Glu Gly Ser Tyr Leu
1140 1145 1150

Val Thr Gly Gly Leu Gly Ala Leu Gly Leu Leu Val Ala Arg Trp Leu
1155 1160 1165

Val Glu Arg Gly Ala Gly His Leu Val Leu Ile Ser Arg His Gly Leu
1170 1175 1180

Pro Asp Arg Glu Glu Trp Gly Arg Asp Gln Pro Pro Glu Val Arg Ala
1185 1190 1195 1200

Arg Ile Ala Ala Ile Glu Ala Leu Glu Ala Gln Gly Ala Arg Val Thr
1205 1210 1215

Val Ala Ala Val Asp Val Ala Asp Ala Glu Gly Met Ala Ala Leu Leu
1220 1225 1230

Ala Ala Val Glu Pro Pro Leu Arg Gly Val Val His Ala Ala Gly Leu
1235 1240 1245

Leu Asp Asp Gly Leu Leu Ala His Gln Asp Ala Gly Arg Leu Ala Arg
1250 1255 1260

Val Leu Arg Pro Lys Val Glu Gly Ala Trp Val Leu His Thr Leu Thr
1265 1270 1275 1280

Arg Glu Gln Pro Leu Asp Leu Phe Val Leu Phe Ser Ser Ala Ser Gly
1285 1290 1295

Val Phe Gly Ser Ile Gly Gln Gly Ser Tyr Ala Ala Gly Asn Ala Phe
1300 1305 1310

Leu Asp Ala Leu Ala Asp Leu Arg Arg Thr Gln Gly Leu Ala Ala Leu
1315 1320 1325

Ser Ile Ala Trp Gly Leu Trp Ala Glu Gly Gly Met Gly Ser Gln Ala
1330 1335 1340

Gln Arg Arg Glu His Glu Ala Ser Gly Ile Trp Ala Met Pro Thr Ser
1345 1350 1355 1360

Arg Ala Leu Ala Ala Met Glu Trp Leu Leu Gly Thr Arg Ala Thr Gln
1365 1370 1375

Arg Val Val Ile Gln Met Asp Trp Ala His Ala Gly Ala Ala Pro Arg
1380 1385 1390

Asp Ala Ser Arg Gly Arg Phe Trp Asp Arg Leu Val Thr Ala Thr Lys
1395 1400 1405

Glu Ala Ser Ser Ser Ala Val Pro Ala Val Glu Arg Trp Arg Asn Ala
1410 1415 1420

Ser Val Val Glu Thr Arg Ser Ala Leu Tyr Glu Leu Val Arg Gly Val
1425 1430 1435 1440

Val Ala Gly Val Met Gly Phe Thr Asp Gln Gly Thr Leu Asp Val Arg
1445 1450 1455

Arg Gly Phe Ala Glu Gln Gly Leu Asp Ser Leu Met Ala Val Glu Ile
1460 1465 1470

Arg Lys Arg Leu Gln Gly Glu Leu Gly Met Pro Leu Ser Ala Thr Leu
1475 1480 1485

Ala Phe Asp His Pro Thr Val Glu Arg Leu Val Glu Tyr Leu Leu Ser
1490 1495 1500

Gln Ala Leu Glu Leu Gln Asp Arg Thr Asp Val Arg Ser Val Arg Leu
1505 1510 1515 1520

Pro Ala Thr Glu Asp Pro Ile Ala Ile Val Gly Ala Ala Cys Arg Phe
1525 1530 1535

Pro Gly Gly Val Glu Asp Leu Glu Ser Tyr Trp Gln Leu Leu Thr Glu
1540 1545 1550

Gly Val Val Val Ser Thr Glu Val Pro Ala Asp Arg Trp Asn Gly Ala
1555 1560 1565

Asp Gly Arg Val Pro Gly Ser Gly Glu Ala Gln Arg Gln Thr Tyr Val
1570 1575 1580

Pro Arg Gly Gly Phe Leu Arg Glu Val Glu Thr Phe Asp Ala Ala Phe
1585 1590 1595 1600

Phe His Ile Ser Pro Arg Glu Ala Met Ser Leu Asp Pro Gln Gln Arg
1605 1610 1615

Leu Leu Leu Glu Val Ser Trp Glu Ala Ile Glu Arg Ala Gly Gln Asp
1620 1625 1630

Pro Ser Ala Leu Arg Glu Ser Pro Thr Gly Val Phe Val Gly Ala Gly
1635 1640 1645

Pro Asn Glu Tyr Ala Glu Arg Val Gln Glu Leu Ala Asp Glu Ala Ala
1650 1655 1660

Gly Leu Tyr Ser Gly Thr Gly Asn Met Leu Ser Val Ala Ala Gly Arg
1665 1670 1675 1680

Leu Ser Phe Phe Leu Gly Leu His Gly Pro Thr Leu Ala Val Asp Thr
1685 1690 1695

Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Gly Cys Gln Ser Leu
1700 1705 1710

Arg Arg Gly Glu Cys Asp Gln Ala Leu Val Gly Gly Val Asn Met Leu
1715 1720 1725

Leu Ser Pro Lys Thr Phe Ala Leu Leu Ser Arg Met His Ala Leu Ser
1730 1735 1740

Pro Gly Gly Arg Cys Lys Thr Phe Ser Ala Asp Ala Asp Gly Tyr Ala
1745 1750 1755 1760

Arg Ala Glu Gly Cys Ala Val Val Val Leu Lys Arg Leu Ser Asp Ala

1765 1770 1775

Gln Arg Asp Arg Asp Pro Ile Leu Ala Val Ile Arg Gly Thr Ala Ile
1780 1785 1790

Asn His Asp Gly Pro Ser Ser Gly Leu Thr Val Pro Ser Gly Pro Ala
1795 1800 1805

Gln Glu Ala Leu Leu Arg Gln Ala Leu Ala His Ala Gly Val Val Pro
1810 1815 1820

Ala Asp Val Asp Phe Val Glu Cys His Gly Thr Gly Thr Ala Leu Gly
1825 1830 1835 1840

Asp Pro Ile Glu Val Arg Ala Leu Ser Asp Val Tyr Gly Gln Ala Arg
1845 1850 1855

Pro Ala Asp Arg Pro Leu Ile Leu Gly Ala Ala Lys Ala Asn Leu Gly
1860 1865 1870

His Met Glu Pro Ala Ala Gly Leu Ala Gly Leu Leu Lys Ala Val Leu
1875 1880 1885

Ala Leu Gly Gln Glu Gln Ile Pro Ala Gln Pro Glu Leu Gly Glu Leu
1890 1895 1900

Asn Pro Leu Leu Pro Trp Glu Ala Leu Pro Val Ala Val Ala Arg Ala
1905 1910 1915 1920

Ala Val Pro Trp Pro Arg Thr Asp Arg Pro Arg Phe Ala Gly Val Ser
1925 1930 1935

Ser Phe Gly Met Ser Gly Thr Asn Ala His Val Val Leu Glu Glu Ala
1940 1945 1950

Pro Ala Val Glu Leu Trp Pro Ala Ala Pro Glu Arg Ser Ala Glu Leu
1955 1960 1965

Leu Val Leu Ser Gly Lys Ser Glu Gly Ala Leu Asp Ala Gln Ala Ala
1970 1975 1980

Arg Leu Arg Glu His Leu Asp Met His Pro Glu Leu Gly Leu Gly Asp
1985 1990 1995 2000

Val Ala Phe Ser Leu Ala Thr Thr Arg Ser Ala Met Asn His Arg Leu
2005 2010 2015

Ala Val Ala Val Thr Ser Arg Glu Gly Leu Leu Ala Ala Leu Ser Ala
2020 2025 2030

Val Ala Gln Gly Gln Thr Pro Pro Gly Ala Ala Arg Cys Ile Ala Ser
2035 2040 2045

Ser Ser Arg Gly Lys Leu Ala Phe Leu Phe Thr Gly Gln Gly Ala Gln
2050 2055 2060

Thr Pro Gly Met Gly Arg Gly Leu Cys Ala Ala Trp Pro Ala Phe Arg
2065 2070 2075 2080

Glu Ala Phe Asp Arg Cys Val Ala Leu Phe Asp Arg Glu Leu Asp Arg
2085 2090 2095

Pro Leu Arg Glu Val Met Trp Ala Glu Pro Gly Ser Ala Glu Ser Leu
2100 2105 2110

Leu Leu Asp Gln Thr Ala Phe Thr Gln Pro Ala Leu Phe Thr Val Glu
2115 2120 2125

Tyr Ala Leu Thr Ala Leu Trp Arg Ser Trp Gly Val Glu Pro Glu Leu
2130 2135 2140

Val Ala Gly His Ser Ala Gly Glu Leu Val Ala Ala Cys Val Ala Gly
2145 2150 2155 2160

Val Phe Ser Leu Glu Asp Gly Val Arg Leu Val Ala Ala Arg Gly Arg
2165 2170 2175

Leu Met Gln Gly Leu Ser Ala Gly Gly Ala Met Val Ser Leu Gly Ala
2180 2185 2190

Pro Glu Ala Glu Val Ala Ala Ala Val Ala Pro His Ala Ala Ser Val
2195 2200 2205

Ser Ile Ala Ala Val Asn Gly Pro Glu Gln Val Val Ile Ala Gly Val
2210 2215 2220

Glu Gln Ala Val Gln Ala Ile Ala Ala Gly Phe Ala Ala Arg Gly Ala
2225 2230 2235 2240

Arg Thr Lys Arg Leu His Val Ser His Ala Ser His Ser Pro Leu Met
2245 2250 2255

Glu Pro Met Leu Glu Glu Phe Gly Arg Val Ala Ala Ser Val Thr Tyr
2260 2265 2270

Arg Arg Pro Ser Val Ser Leu Val Ser Asn Leu Ser Gly Lys Val Val
2275 2280 2285

Ala Asp Glu Leu Ser Ala Pro Gly Tyr Trp Val Arg His Val Arg Glu
2290 2295 2300

Ala Val Arg Phe Ala Asp Gly Val Lys Ala Leu His Glu Ala Gly Ala
2305 2310 2315 2320

Gly Thr Phe Val Glu Val Gly Pro Lys Pro Thr Leu Leu Gly Leu Leu
2325 2330 2335

Pro Ala Cys Leu Pro Glu Ala Glu Pro Thr Leu Leu Ala Ser Leu Arg
2340 2345 2350

Ala Gly Arg Glu Glu Ala Ala Gly Val Leu Glu Ala Leu Gly Arg Leu
2355 2360 2365

Trp Ala Ala Gly Gly Ser Val Ser Trp Pro Gly Val Phe Pro Thr Ala
2370 2375 2380

Gly Arg Arg Val Pro Leu Pro Thr Tyr Pro Trp Gln Arg Gln Arg Tyr
2385 2390 2395 2400

Trp Pro Asp Ile Glu Pro Asp Ser Arg Arg His Ala Ala Ala Asp Pro
2405 2410 2415

Thr Gln Gly Trp Phe Tyr Arg Val Asp Trp Pro Glu Ile Pro Arg Ser
2420 2425 2430

Leu Gln Lys Ser Glu Glu Ala Ser Arg Gly Ser Trp Leu Val Leu Ala
2435 2440 2445

Asp Lys Gly Gly Val Gly Glu Ala Val Ala Ala Ala Leu Ser Thr Arg
2450 2455 2460

Gly Leu Pro Cys Val Val Leu His Ala Pro Ala Glu Thr Ser Ala Thr
2465 2470 2475 2480

Ala Glu Leu Val Thr Glu Ala Ala Gly Gly Arg Ser Asp Trp Gln Val
2485 2490 2495

Val Leu Tyr Leu Trp Gly Leu Asp Ala Val Val Gly Ala Glu Ala Ser
2500 2505 2510

Ile Asp Glu Ile Gly Asp Ala Thr Arg Arg Ala Thr Ala Pro Val Leu
2515 2520 2525

Gly Leu Ala Arg Phe Leu Ser Thr Val Ser Cys Ser Pro Arg Leu Trp
2530 2535 2540

Val Val Thr Arg Gly Ala Cys Ile Val Gly Asp Glu Pro Ala Ile Ala
2545 2550 2555 2560

Pro Cys Gln Ala Ala Leu Trp Gly Met Gly Arg Val Ala Ala Leu Glu
2565 2570 2575

His Pro Gly Ala Trp Gly Gly Leu Val Asp Leu Asp Pro Arg Ala Ser
2580 2585 2590

Pro Pro Gln Ala Ser Pro Ile Asp Gly Glu Met Leu Val Thr Glu Leu
2595 2600 2605

Leu Ser Gln Glu Thr Glu Asp Gln Leu Ala Phe Arg His Gly Arg Arg
2610 2615 2620

His Ala Ala Arg Leu Val Ala Ala Pro Pro Gln Gly Gln Ala Ala Pro
2625 2630 2635 2640

Val Ser Leu Ser Ala Glu Ala Ser Tyr Leu Val Thr Gly Gly Leu Gly
2645 2650 2655

Gly Leu Gly Leu Ile Val Ala Gln Trp Leu Val Glu Leu Gly Ala Arg
2660 2665 2670

His Leu Val Leu Thr Ser Arg Arg Gly Leu Pro Asp Arg Gln Ala Trp
2675 2680 2685

Cys Glu Gln Gln Pro Pro Glu Ile Arg Ala Arg Ile Ala Ala Val Glu
2690 2695 2700

Ala Leu Glu Ala Arg Gly Ala Arg Val Thr Val Ala Ala Val Asp Val
2705 2710 2715 2720

Ala Asp Val Glu Pro Met Thr Ala Leu Val Ser Ser Val Glu Pro Pro
2725 2730 2735

Leu Arg Gly Val Val His Ala Ala Gly Val Ser Val Met Arg Pro Leu
2740 2745 2750

Ala Glu Thr Asp Glu Thr Leu Leu Glu Ser Val Leu Arg Pro Lys Val
2755 2760 2765

Ala Gly Ser Trp Leu Leu His Arg Leu Leu His Gly Arg Pro Leu Asp
2770 2775 2780

Leu Phe Val Leu Phe Ser Ser Gly Ala Ala Val Trp Gly Ser His Ser
2785 2790 2795 2800

Gln Gly Ala Tyr Ala Ala Ala Asn Ala Phe Leu Asp Gly Leu Ala His

2805 2810 2815

Leu Arg Arg Ser Gln Ser Leu Pro Ala Leu Ser Val Ala Trp Gly Leu
2820 2825 2830

Trp Ala Glu Gly Gly Met Ala Asp Ala Glu Ala His Ala Arg Leu Ser
2835 2840 2845

Asp Ile Gly Val Leu Pro Met Ser Thr Ser Ala Ala Leu Ser Ala Leu
2850 2855 2860

Gln Arg Leu Val Glu Thr Gly Ala Ala Gln Arg Thr Val Thr Arg Met
2865 2870 2875 2880

Asp Trp Ala Arg Phe Ala Pro Val Tyr Thr Ala Arg Gly Arg Arg Asn
2885 2890 2895

Leu Leu Ser Ala Leu Val Ala Gly Arg Asp Ile Ile Ala Pro Ser Pro
2900 2905 2910

Pro Ala Ala Ala Thr Arg Asn Trp Arg Gly Leu Ser Val Ala Glu Ala
2915 2920 2925

Arg Val Ala Leu His Glu Ile Val His Gly Ala Val Ala Arg Val Leu
2930 2935 2940

Gly Phe Leu Asp Pro Ser Ala Leu Asp Pro Gly Met Gly Phe Asn Glu
2945 2950 2955 2960

Gln Gly Leu Asp Ser Leu Met Ala Val Glu Ile Arg Asn Leu Leu Gln
2965 2970 2975

Ala Glu Leu Asp Val Arg Leu Ser Thr Thr Leu Ala Phe Asp His Pro
2980 2985 2990

Thr Val Gln Arg Leu Val Glu His Leu Leu Val Asp Val Leu Lys Leu
2995 3000 3005

Glu Asp Arg Ser Asp Thr Gln His Val Arg Ser Leu Ala Ser Asp Glu
3010 3015 3020

Pro Ile Ala Ile Val Gly Ala Ala Cys Arg Phe Pro Gly Gly Val Glu
3025 3030 3035 3040

Asp Leu Glu Ser Tyr Trp Gln Leu Leu Ala Glu Gly Val Val Val Ser
3045 3050 3055

Ala Glu Val Pro Ala Asp Arg Trp Asp Ala Ala Asp Trp Tyr Asp Pro
3060 3065 3070

Asp Pro Glu Ile Pro Gly Arg Thr Tyr Val Thr Lys Gly Ala Phe Leu
3075 3080 3085

Arg Asp Leu Gln Arg Leu Asp Ala Thr Phe Phe Arg Ile Ser Pro Arg
3090 3095 3100

Glu Ala Met Ser Leu Asp Pro Gln Gln Arg Leu Leu Leu Glu Val Ser
3105 3110 3115 3120

Trp Glu Ala Leu Glu Ser Ala Gly Ile Ala Pro Asp Thr Leu Arg Asp
3125 3130 3135

Ser Pro Thr Gly Val Phe Val Gly Ala Gly Pro Asn Glu Tyr Tyr Thr
3140 3145 3150

Gln Arg Leu Arg Gly Phe Thr Asp Gly Ala Ala Gly Leu Tyr Gly Gly
3155 3160 3165

Thr Gly Asn Met Leu Ser Val Thr Ala Gly Arg Leu Ser Phe Phe Leu
3170 3175 3180

Gly Leu His Gly Pro Thr Leu Ala Met Asp Thr Ala Cys Ser Ser Ser
3185 3190 3195 3200

Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Leu Gly Glu Cys
3205 3210 3215

Asp Gln Ala Leu Val Gly Gly Val Asn Val Leu Leu Ala Pro Glu Thr
3220 3225 3230

Phe Val Leu Leu Ser Arg Met Arg Ala Leu Ser Pro Asp Gly Arg Cys
3235 3240 3245

Lys Thr Phe Ser Ala Asp Ala Asp Gly Tyr Ala Arg Gly Glu Gly Cys
3250 3255 3260

Ala Val Val Val Leu Lys Arg Leu Arg Asp Ala Gln Arg Ala Gly Asp
3265 3270 3275 3280

Ser Ile Leu Ala Leu Ile Arg Gly Ser Ala Val Asn His Asp Gly Pro
3285 3290 3295

Ser Ser Gly Leu Thr Val Pro Asn Gly Pro Ala Gln Gln Ala Leu Leu
3300 3305 3310

Arg Gln Ala Leu Ser Gln Ala Gly Val Ser Pro Val Asp Val Asp Phe
3315 3320 3325

Val Glu Cys His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu Val
3330 3335 3340

Gln Ala Leu Ser Glu Val Tyr Gly Pro Gly Arg Ser Gly Asp Arg Pro
3345 3350 3355 3360

Leu Val Leu Gly Ala Ala Lys Ala Asn Val Ala His Leu Glu Ala Ala
3365 3370 3375

Ser Gly Leu Ala Ser Leu Leu Lys Ala Val Leu Ala Leu Arg His Glu
3380 3385 3390

Gln Ile Pro Ala Gln Pro Glu Leu Gly Glu Leu Asn Pro His Leu Pro
3395 3400 3405

Trp Asn Thr Leu Pro Val Ala Val Pro Arg Lys Ala Val Pro Trp Gly
3410 3415 3420

Arg Gly Ala Arg Pro Arg Arg Ala Gly Val Ser Ala Phe Gly Leu Ser
3425 3430 3435 3440

Gly Thr Asn Val His Val Val Leu Glu Glu Ala Pro Glu Val Glu Pro
3445 3450 3455

Ala Pro Ala Ala Pro Ala Arg Pro Val Glu Leu Val Val Leu Ser Ala
3460 3465 3470

Lys Ser Ala Ala Ala Leu Asp Ala Ala Ala Ala Arg Leu Ser Ala His
3475 3480 3485

Leu Ser Ala His Pro Glu Leu Ser Leu Gly Asp Val Ala Phe Ser Leu
3490 3495 3500

Ala Thr Thr Arg Ser Pro Met Glu His Arg Leu Ala Ile Ala Thr Thr
3505 3510 3515 3520

Ser Arg Glu Ala Leu Arg Gly Ala Leu Asp Ala Ala Ala Gln Gln Lys
3525 3530 3535

Thr Pro Gln Gly Ala Val Arg Gly Lys Ala Val Ser Ser Arg Gly Lys
3540 3545 3550

Leu Ala Phe Leu Phe Thr Gly Gln Gly Ala Gln Met Pro Gly Met Gly
3555 3560 3565

Arg Gly Leu Tyr Glu Thr Trp Pro Ala Phe Arg Glu Ala Phe Asp Arg
3570 3575 3580

Cys Val Ala Leu Phe Asp Arg Glu Ile Asp Gln Pro Leu Arg Glu Val
3585 3590 3595 3600

Met Trp Ala Ala Pro Gly Leu Ala Gln Ala Ala Arg Leu Asp Gln Thr
3605 3610 3615

Ala Tyr Ala Gln Pro Ala Leu Phe Ala Leu Glu Tyr Ala Leu Ala Ala
3620 3625 3630

Leu Trp Arg Ser Trp Gly Val Glu Pro His Val Leu Leu Gly His Ser
3635 3640 3645

Ile Gly Glu Leu Val Ala Ala Cys Val Ala Gly Val Phe Ser Leu Glu
3650 3655 3660

Asp Ala Val Arg Leu Val Ala Ala Arg Gly Arg Leu Met Gln Ala Leu
3665 3670 3675 3680

Pro Ala Gly Gly Ala Met Val Ala Ile Ala Ala Ser Glu Ala Glu Val
3685 3690 3695

Ala Ala Ser Val Ala Pro His Ala Ala Thr Val Ser Ile Ala Ala Val
3700 3705 3710

Asn Gly Pro Asp Ala Val Val Ile Ala Gly Ala Glu Val Gln Val Leu
3715 3720 3725

Ala Leu Gly Ala Thr Phe Ala Ala Arg Gly Ile Arg Thr Lys Arg Leu
3730 3735 3740

Ala Val Ser His Ala Phe His Ser Pro Leu Met Asp Pro Met Leu Glu
3745 3750 3755 3760

Asp Phe Gln Arg Val Ala Ala Thr Ile Ala Tyr Arg Ala Pro Asp Arg
3765 3770 3775

Pro Val Val Ser Asn Val Thr Gly His Val Ala Gly Pro Glu Ile Ala
3780 3785 3790

Thr Pro Glu Tyr Trp Val Arg His Val Arg Ser Ala Val Arg Phe Gly
3795 3800 3805

Asp Gly Ala Lys Ala Leu His Ala Ala Gly Ala Ala Thr Phe Val Glu
3810 3815 3820

Val Gly Pro Lys Pro Val Leu Leu Gly Leu Leu Pro Ala Cys Leu Gly
3825 3830 3835 3840

Glu Ala Asp Ala Val Leu Val Pro Ser Leu Arg Ala Asp Arg Ser Glu

3845 3850 3855

Cys Glu Val Val Leu Ala Ala Leu Gly Ala Trp Tyr Ala Trp Gly Gly
3860 3865 3870

Ala Leu Asp Trp Lys Gly Val Phe Pro Asp Gly Ala Arg Arg Val Ala
3875 3880 3885

Leu Pro Met Tyr Pro Trp Gln Arg Glu Arg His Trp Met Asp Leu Thr
3890 3895 3900

Pro Arg Ser Ala Ala Pro Ala Gly Ile Ala Gly Arg Trp Pro Leu Ala
3905 3910 3915 3920

Gly Val Gly Leu Cys Met Pro Gly Ala Val Leu His His Val Leu Ser
3925 3930 3935

Ile Gly Pro Arg His Gln Pro Phe Leu Gly Asp His Leu Val Phe Gly
3940 3945 3950

Lys Val Val Val Pro Gly Ala Phe His Val Ala Val Ile Leu Ser Ile
3955 3960 3965

Ala Ala Glu Arg Trp Pro Glu Arg Ala Ile Glu Leu Thr Gly Val Glu
3970 3975 3980

Phe Leu Lys Ala Ile Ala Met Glu Pro Asp Gln Glu Val Glu Leu His
3985 3990 3995 4000

Ala Val Leu Thr Pro Glu Ala Ala Gly Asp Gly Tyr Leu Phe Glu Leu
4005 4010 4015

Ala Thr Leu Ala Ala Pro Glu Thr Glu Arg Arg Trp Thr Thr His Ala
4020 4025 4030

Arg Gly Arg Val Gln Pro Thr Asp Gly Ala Pro Gly Ala Leu Pro Arg
4035 4040 4045

Leu Glu Val Leu Glu Asp Arg Ala Ile Gln Pro Leu Asp Phe Ala Gly
4050 4055 4060

Phe Leu Asp Arg Leu Ser Ala Val Arg Ile Gly Trp Gly Pro Leu Trp
4065 4070 4075 4080

Arg Trp Leu Gln Asp Gly Arg Val Gly Asp Glu Ala Ser Leu Ala Thr
4085 4090 4095

Leu Val Pro Thr Tyr Pro Asn Ala His Asp Val Ala Pro Leu His Pro
4100 4105 4110

Ile Leu Leu Asp Asn Gly Phe Ala Val Ser Leu Leu Ser Thr Arg Ser
4115 4120 4125

Glu Pro Glu Asp Asp Gly Thr Pro Pro Leu Pro Phe Ala Val Glu Arg
4130 4135 4140

Val Arg Trp Trp Arg Ala Pro Val Gly Arg Val Arg Cys Gly Gly Val
4145 4150 4155 4160

Pro Arg Ser Gln Ala Phe Gly Val Ser Ser Phe Val Leu Val Asp Glu
4165 4170 4175

Thr Gly Glu Val Val Ala Glu Val Glu Gly Phe Val Cys Arg Arg Ala
4180 4185 4190

Pro Arg Glu Val Phe Leu Arg Gln Glu Ser Gly Ala Ser Thr Ala Ala
4195 4200 4205

Leu Tyr Arg Leu Asp Trp Pro Glu Ala Pro Leu Pro Asp Ala Pro Ala
4210 4215 4220

Glu Arg Ile Glu Glu Ser Trp Val Val Val Ala Ala Pro Gly Ser Glu
4225 4230 4235 4240

Met Ala Ala Ala Leu Ala Thr Arg Leu Asn Arg Cys Val Leu Ala Glu
4245 4250 4255

Pro Lys Gly Leu Glu Ala Ala Leu Ala Gly Val Ser Pro Ala Gly Val
4260 4265 4270

Ile Cys Leu Trp Glu Ala Gly Ala His Glu Glu Ala Pro Ala Ala Ala
4275 4280 4285

Gln Arg Val Ala Thr Glu Gly Leu Ser Val Val Gln Ala Leu Arg Asp
4290 4295 4300

Arg Ala Val Arg Leu Trp Trp Val Thr Met Gly Ala Val Ala Val Glu
4305 4310 4315 4320

Ala Gly Glu Arg Val Gln Val Ala Thr Ala Pro Val Trp Gly Leu Gly
4325 4330 4335

Arg Thr Val Met Gln Glu Arg Pro Glu Leu Ser Cys Thr Leu Val Asp
4340 4345 4350

Leu Glu Pro Glu Ala Asp Ala Ala Arg Ser Ala Asp Val Leu Leu Arg
4355 4360 4365

Glu Leu Gly Arg Ala Asp Asp Glu Thr Gln Val Ala Phe Arg Ser Gly
4370 4375 4380

Lys Arg Arg Val Ala Arg Leu Val Lys Ala Thr Thr Pro Glu Gly Leu
4385 4390 4395 4400

Leu Val Pro Asp Ala Glu Ser Tyr Arg Leu Glu Ala Gly Gln Lys Gly
4405 4410 4415

Thr Leu Asp Gln Leu Arg Leu Ala Pro Ala Gln Arg Arg Ala Pro Gly
4420 4425 4430

Pro Gly Glu Val Glu Ile Lys Val Thr Ala Ser Gly Leu Asn Phe Arg
4435 4440 4445

Thr Val Leu Ala Val Leu Gly Met Tyr Pro Gly Asp Ala Gly Pro Met
4450 4455 4460

Gly Gly Asp Cys Ala Gly Val Ala Thr Ala Val Gly Gln Gly Val Arg
4465 4470 4475 4480

His Val Ala Val Gly Asp Ala Val Met Thr Leu Gly Thr Leu His Arg
4485 4490 4495

Phe Val Thr Val Asp Ala Arg Leu Val Val Arg Gln Pro Ala Gly Leu
4500 4505 4510

Thr Pro Ala Gln Ala Ala Thr Val Pro Val Ala Phe Leu Thr Ala Trp
4515 4520 4525

Leu Ala Leu His Asp Leu Gly Asn Leu Arg Arg Gly Glu Arg Val Leu
4530 4535 4540

Ile His Ala Ala Ala Gly Gly Val Gly Met Ala Ala Val Gln Ile Ala
4545 4550 4555 4560

Arg Trp Ile Gly Ala Glu Val Phe Ala Thr Ala Ser Pro Ser Lys Trp
4565 4570 4575

Ala Ala Val Gln Ala Met Gly Val Pro Arg Thr His Ile Ala Ser Ser
4580 4585 4590

Arg Thr Leu Glu Phe Ala Glu Thr Phe Arg Gln Val Thr Gly Gly Arg
4595 4600 4605

Gly Val Asp Val Val Leu Asn Ala Leu Ala Gly Glu Phe Val Asp Ala
4610 4615 4620

Ser Leu Ser Leu Leu Ser Thr Gly Gly Arg Phe Leu Glu Met Gly Lys
4625 4630 4635 4640

Thr Asp Ile Arg Asp Arg Ala Ala Val Ala Ala Ala His Pro Gly Val
4645 4650 4655

Arg Tyr Arg Val Phe Asp Ile Leu Glu Leu Ala Pro Asp Arg Thr Arg
4660 4665 4670

Glu Ile Leu Glu Arg Val Val Glu Gly Phe Ala Ala Gly His Leu Arg
4675 4680 4685

Ala Leu Pro Val His Ala Phe Ala Ile Thr Lys Ala Glu Ala Ala Phe
4690 4695 4700

Arg Phe Met Ala Gln Ala Arg His Gln Gly Lys Val Val Leu Leu Pro
4705 4710 4715 4720

Ala Pro Ser Ala Ala Pro Leu Ala Pro Thr Gly Thr Val Leu Leu Thr
4725 4730 4735

Gly Gly Leu Gly Ala Leu Gly Leu His Val Ala Arg Trp Leu Ala Gln
4740 4745 4750

Gln Gly Val Pro His Met Val Leu Thr Gly Arg Arg Gly Leu Asp Thr
4755 4760 4765

Pro Gly Ala Ala Lys Ala Val Ala Glu Ile Glu Ala Leu Gly Ala Arg
4770 4775 4780

Val Thr Ile Ala Ala Ser Asp Val Ala Asp Arg Asn Ala Leu Glu Ala
4785 4790 4795 4800

Val Leu Gln Ala Ile Pro Ala Glu Trp Pro Leu Gln Gly Val Ile His
4805 4810 4815

Ala Ala Gly Ala Leu Asp Asp Gly Val Leu Asp Glu Gln Thr Thr Asp
4820 4825 4830

Arg Phe Ser Arg Val Leu Ala Pro Lys Val Thr Gly Ala Trp Asn Leu
4835 4840 4845

His Glu Leu Thr Ala Gly Asn Asp Leu Ala Phe Phe Val Leu Phe Ser
4850 4855 4860

Ser Met Ser Gly Leu Leu Gly Ser Ala Gly Gln Ser Asn Tyr Ala Ala
4865 4870 4875 4880

Ala Asn Thr Phe Leu Asp Ala Leu Ala Ala His Arg Arg Ala Glu Gly

4885 4890 4895

Leu Ala Ala Gln Ser Leu Ala Trp Gly Pro Trp Ser Asp Gly Gly Met
4900 4905 4910

Ala Ala Gly Leu Ser Ala Ala Leu Gln Ala Arg Leu Ala Arg His Gly
4915 4920 4925

Met Gly Ala Leu Ser Pro Ala Gln Gly Thr Ala Leu Leu Gly Gln Ala
4930 4935 4940

Leu Ala Arg Pro Glu Thr Gln Leu Gly Ala Met Ser Leu Asp Val Arg
4945 4950 4955 4960

Ala Ala Ser Gln Ala Ser Gly Ala Ala Val Pro Pro Val Trp Arg Ala
4965 4970 4975

Leu Val Arg Ala Glu Ala Arg His Thr Ala Ala Gly Ala Gln Gly Ala
4980 4985 4990

Leu Ala Ala Arg Leu Gly Ala Leu Pro Glu Ala Arg Arg Ala Asp Glu
4995 5000 5005

Val Arg Lys Val Val Gln Ala Glu Ile Ala Arg Val Leu Ser Trp Ser
5010 5015 5020

Ala Ala Ser Ala Val Pro Val Asp Arg Pro Leu Ser Asp Leu Gly Leu
5025 5030 5035 5040

Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Val Leu Gly Gln Arg Val
5045 5050 5055

Gly Ala Thr Leu Pro Ala Thr Leu Ala Phe Asp His Pro Thr Val Asp
5060 5065 5070

Ala Leu Thr Arg Trp Leu Leu Asp Lys Val Leu Ala Val Ala Glu Pro
5075 5080 5085

Ser Val Ser Ser Ala Lys Ser Ser Pro Gln Val Ala Leu Asp Glu Pro
5090 5095 5100

Ile Ala Ile Ile Gly Ile Gly Cys Arg Phe Pro Gly Gly Val Ala Asp
5105 5110 5115 5120

Pro Glu Ser Phe Trp Arg Leu Leu Glu Glu Gly Ser Asp Ala Val Val
5125 5130 5135

Glu Val Pro His Glu Arg Trp Asp Ile Asp Ala Phe Tyr Asp Pro Asp
5140 5145 5150

Pro Asp Val Arg Gly Lys Met Thr Thr Arg Phe Gly Gly Phe Leu Ser
5155 5160 5165

Asp Ile Asp Arg Phe Asp Pro Ala Phe Phe Gly Ile Ser Pro Arg Glu
5170 5175 5180

Ala Thr Thr Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Thr Ser Trp
5185 5190 5195 5200

Glu Ala Phe Glu Arg Ala Gly Ile Leu Pro Glu Arg Leu Met Gly Ser
5205 5210 5215

Asp Thr Gly Val Phe Val Gly Leu Phe Tyr Gln Glu Tyr Ala Ala Leu
5220 5225 5230

Ala Gly Gly Ile Glu Ala Phe Asp Gly Tyr Leu Gly Thr Gly Thr Thr
5235 5240 5245

Ala Ser Val Ala Ser Gly Arg Ile Ser Tyr Val Leu Gly Leu Lys Gly
5250 5255 5260

Pro Ser Leu Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Val
5265 5270 5275 5280

His Leu Ala Cys Gln Ala Leu Arg Arg Gly Glu Cys Ser Val Ala Leu
5285 5290 5295

Ala Gly Gly Val Ala Leu Met Leu Thr Pro Ala Thr Phe Val Glu Phe
5300 5305 5310

Ser Arg Leu Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ser
5315 5320 5325

Ala Ala Ala Asp Gly Val Gly Trp Ser Glu Gly Cys Ala Met Leu Leu
5330 5335 5340

Leu Lys Pro Leu Arg Asp Ala Gln Arg Asp Gly Asp Pro Ile Leu Ala
5345 5350 5355 5360

Val Ile Arg Gly Thr Ala Val Asn Gln Asp Gly Arg Ser Asn Gly Leu
5365 5370 5375

Thr Ala Pro Asn Gly Ser Ser Gln Gln Glu Val Ile Arg Arg Ala Leu
5380 5385 5390

Glu Gln Ala Gly Leu Ala Pro Ala Asp Val Ser Tyr Val Glu Cys His
5395 5400 5405

Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile Glu Val Gln Ala Leu Gly
5410 5415 5420

Ala Val Leu Ala Gln Gly Arg Pro Ser Asp Arg Pro Leu Val Ile Gly
5425 5430 5435 5440

Ser Val Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala
5445 5450 5455

Gly Val Ile Lys Val Ala Leu Ala Leu Glu Arg Gly Leu Ile Pro Arg
5460 5465 5470

Ser Leu His Phe Asp Ala Pro Asn Pro His Ile Pro Trp Ser Glu Leu
5475 5480 5485

Ala Val Gln Val Ala Ala Lys Pro Val Glu Trp Thr Arg Asn Gly Val
5490 5495 5500

Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser Gly Thr Asn Ala
5505 5510 5515 5520

His Val Val Leu Glu Glu Ala Pro Ala Ala Ala Phe Ala Pro Ala Ala
5525 5530 5535

Ala Arg Ser Ala Glu Leu Phe Val Leu Ser Ala Lys Ser Ala Ala Ala
5540 5545 5550

Leu Asp Ala Gln Ala Ala Arg Leu Ser Ala His Val Val Ala His Pro
5555 5560 5565

Glu Leu Gly Leu Gly Asp Leu Ala Phe Ser Leu Ala Thr Thr Arg Ser
5570 5575 5580

Pro Met Thr Tyr Arg Leu Ala Val Ala Ala Thr Ser Arg Glu Ala Leu
5585 5590 5595 5600

Ser Ala Ala Leu Asp Thr Ala Ala Gln Gly Gln Ala Pro Pro Ala Ala
5605 5610 5615

Ala Arg Gly His Ala Ser Thr Gly Ser Ala Pro Lys Val Val Phe Val
5620 5625 5630

Phe Pro Gly Gln Gly Ser Gln Trp Leu Gly Met Gly Gln Lys Leu Leu
5635 5640 5645

Ser Glu Glu Pro Val Phe Arg Asp Ala Leu Ser Ala Cys Asp Arg Ala
5650 5655 5660

Ile Gln Ala Glu Ala Gly Trp Ser Leu Leu Ala Glu Leu Ala Ala Asp
5665 5670 5675 5680

Glu Thr Thr Ser Gln Leu Gly Arg Ile Asp Val Val Gln Pro Ala Leu
5685 5690 5695

Phe Ala Ile Glu Val Ala Leu Ser Ala Leu Trp Arg Ser Trp Gly Val
5700 5705 5710

Glu Pro Asp Ala Val Val Gly His Ser Met Gly Glu Val Ala Ala Ala
5715 5720 5725

His Val Ala Gly Ala Leu Ser Leu Glu Asp Ala Val Ala Ile Ile Cys
5730 5735 5740

Arg Arg Ser Leu Leu Leu Arg Arg Ile Ser Gly Gln Gly Glu Met Ala
5745 5750 5755 5760

Val Val Glu Leu Ser Leu Ala Glu Ala Glu Ala Ala Leu Leu Gly Tyr
5765 5770 5775

Glu Asp Arg Leu Ser Val Ala Val Ser Asn Ser Pro Arg Ser Thr Val
5780 5785 5790

Leu Ala Gly Glu Pro Ala Ala Leu Ala Glu Val Leu Ala Ile Leu Ala
5795 5800 5805

Ala Lys Gly Val Phe Cys Arg Arg Val Lys Val Asp Val Ala Ser His
5810 5815 5820

Ser Pro Gln Ile Asp Pro Leu Arg Asp Glu Leu Leu Ala Ala Leu Gly
5825 5830 5835 5840

Glu Leu Glu Pro Arg Gln Ala Thr Val Ser Met Arg Ser Thr Val Thr
5845 5850 5855

Ser Thr Ile Met Ala Gly Pro Glu Leu Val Ala Ser Tyr Trp Ala Asp
5860 5865 5870

Asn Val Arg Gln Pro Val Arg Phe Ala Glu Ala Val Gln Ser Leu Met
5875 5880 5885

Glu Asp Gly His Gly Leu Phe Val Glu Met Ser Pro His Pro Ile Leu
5890 5895 5900

Thr Thr Ser Val Glu Glu Ile Arg Arg Ala Thr Lys Arg Glu Gly Val
5905 5910 5915 5920

Ala Val Gly Ser Leu Arg Arg Gly Gln Asp Glu Arg Leu Ser Met Leu

5925 5930 5935

Glu Ala Leu Gly Ala Leu Trp Val His Gly Gln Ala Val Gly Trp Glu
5940 5945 5950

Arg Leu Phe Ser Ala Gly Gly Ala Gly Leu Arg Arg Val Pro Leu Pro
5955 5960 5965

Thr Tyr Pro Trp Gln Arg Glu Arg Tyr Trp Val Asp Ala Pro Thr Gly
5970 5975 5980

Gly Ala Ala Gly Gly Ser Arg Phe Ala His Ala Gly Ser His Pro Leu
5985 5990 5995 6000

Leu Gly Glu Met Gln Thr Leu Ser Thr Gln Arg Ser Thr Arg Val Trp
6005 6010 6015

Glu Thr Thr Leu Asp Leu Lys Arg Leu Pro Trp Leu Gly Asp His Arg
6020 6025 6030

Val Gln Gly Ala Val Val Phe Pro Gly Ala Ala Tyr Leu Glu Met Ala
6035 6040 6045

Leu Ser Ser Gly Ala Glu Ala Leu Gly Asp Gly Pro Leu Gln Val Ser
6050 6055 6060

Asp Val Val Leu Ala Glu Ala Leu Ala Phe Ala Asp Asp Thr Pro Ala
6065 6070 6075 6080

Ala Val Gln Val Met Ala Thr Glu Glu Arg Pro Gly Arg Leu Gln Phe
6085 6090 6095

His Val Ala Ser Arg Val Pro Gly His Gly Gly Ala Ala Phe Arg Ser
6100 6105 6110

His Ala Arg Gly Val Leu Arg Gln Ile Glu Arg Ala Glu Val Pro Ala
6115 6120 6125

Arg Leu Asp Leu Ala Ala Leu Arg Ala Arg Leu Gln Ala Ser Ala Pro
6130 6135 6140

Ala Ala Ala Thr Tyr Ala Ala Leu Ala Glu Met Gly Leu Glu Tyr Gly
6145 6150 6155 6160

Pro Ala Phe Gln Gly Leu Val Glu Leu Trp Arg Gly Glu Gly Glu Ala
6165 6170 6175

Leu Gly Arg Val Arg Leu Pro Glu Ala Ala Gly Ser Pro Ala Ala Cys
6180 6185 6190

Arg Leu His Pro Ala Leu Leu Asp Ala Cys Phe His Val Ser Ser Ala
6195 6200 6205

Phe Ala Asp Arg Gly Glu Ala Thr Pro Trp Val Pro Val Glu Ile Gly
6210 6215 6220

Ser Leu Arg Trp Phe Gln Arg Pro Ser Gly Glu Leu Trp Cys His Ala
6225 6230 6235 6240

Arg Ser Val Ser His Gly Lys Pro Thr Pro Asp Arg Arg Ser Thr Asp
6245 6250 6255

Phe Trp Val Val Asp Ser Thr Gly Ala Ile Val Ala Glu Ile Ser Gly
6260 6265 6270

Leu Val Ala Gln Arg Leu Ala Gly Gly Val Arg Arg Arg Glu Glu Asp
6275 6280 6285

Asp Trp Phe Met Glu Pro Ala Trp Glu Pro Thr Ala Val Pro Gly Ser
6290 6295 6300

Glu Val Met Ala Gly Arg Trp Leu Leu Ile Gly Ser Gly Gly Gly Leu
6305 6310 6315 6320

Gly Ala Ala Leu His Ser Ala Leu Thr Glu Ala Gly His Ser Val Val
6325 6330 6335

His Ala Thr Gly Arg Gly Thr Ser Ala Ala Gly Leu Gln Ala Leu Leu
6340 6345 6350

Thr Ala Ser Phe Asp Gly Gln Ala Pro Thr Ser Val Val His Leu Gly
6355 6360 6365

Ser Leu Asp Glu Arg Gly Val Leu Asp Ala Asp Ala Pro Phe Asp Ala
6370 6375 6380

Asp Ala Leu Glu Glu Ser Leu Val Arg Gly Cys Asp Ser Val Leu Trp
6385 6390 6395 6400

Thr Val Gln Ala Val Ala Gly Ala Gly Phe Arg Asp Pro Pro Arg Leu
6405 6410 6415

Trp Leu Val Thr Arg Gly Ala Gln Ala Ile Gly Ala Gly Asp Val Ser
6420 6425 6430

Val Ala Gln Ala Pro Leu Leu Gly Leu Gly Arg Val Ile Ala Leu Glu
6435 6440 6445

His Ala Glu Leu Arg Cys Ala Arg Ile Asp Leu Asp Pro Ala Arg Arg
6450 6455 6460

Asp Gly Glu Val Asp Glu Leu Leu Ala Glu Leu Leu Ala Asp Asp Ala
6465 6470 6475 6480

Glu Glu Glu Val Ala Phe Arg Gly Gly Glu Arg Arg Val Ala Arg Leu
6485 6490 6495

Val Arg Arg Leu Pro Glu Thr Asp Cys Arg Glu Lys Ile Glu Pro Ala
6500 6505 6510

Glu Gly Arg Pro Phe Arg Leu Glu Ile Asp Gly Ser Gly Val Leu Asp
6515 6520 6525

Asp Leu Val Leu Arg Ala Thr Glu Arg Arg Pro Pro Gly Pro Gly Glu
6530 6535 6540

Val Glu Ile Ala Val Glu Ala Ala Gly Leu Asn Phe Leu Asp Val Met
6545 6550 6555 6560

Arg Ala Met Gly Ile Tyr Pro Gly Pro Gly Asp Gly Pro Val Ala Leu
6565 6570 6575

Gly Ala Glu Cys Ser Gly Arg Ile Val Ala Met Gly Glu Gly Val Glu
6580 6585 6590

Ser Leu Arg Ile Gly Gln Asp Val Val Ala Val Ala Pro Phe Ser Phe
6595 6600 6605

Gly Thr His Val Thr Ile Asp Ala Arg Met Leu Ala Pro Arg Pro Ala
6610 6615 6620

Ala Leu Thr Ala Ala Gln Ala Ala Ala Leu Pro Val Ala Phe Met Thr
6625 6630 6635 6640

Ala Trp Tyr Gly Leu Val His Leu Gly Arg Leu Arg Ala Gly Glu Arg
6645 6650 6655

Val Leu Ile His Ser Ala Thr Gly Gly Thr Gly Leu Ala Ala Val Gln
6660 6665 6670

Ile Ala Arg His Leu Gly Ala Glu Ile Phe Ala Thr Ala Gly Thr Pro
6675 6680 6685

Glu Lys Arg Ala Trp Leu Arg Glu Gln Gly Ile Ala His Val Met Asp
6690 6695 6700

Ser Arg Ser Leu Asp Phe Ala Glu Gln Val Leu Ala Ala Thr Lys Gly
6705 6710 6715 6720

Glu Gly Val Asp Val Val Leu Asn Ser Leu Ser Gly Ala Ala Ile Asp
6725 6730 6735

Ala Ser Leu Ser Thr Leu Val Pro Asp Gly Arg Phe Ile Glu Leu Gly
6740 6745 6750

Lys Thr Asp Ile Tyr Ala Asp Arg Ser Leu Gly Leu Ala His Phe Arg
6755 6760 6765

Lys Ser Leu Ser Tyr Ser Ala Val Asp Leu Ala Gly Leu Ala Val Arg
6770 6775 6780

Arg Pro Glu Arg Val Ala Ala Leu Leu Ala Glu Val Val Asp Leu Leu
6785 6790 6795 6800

Ala Arg Gly Ala Leu Gln Pro Leu Pro Val Glu Ile Phe Pro Leu Ser
6805 6810 6815

Arg Ala Ala Asp Ala Phe Arg Lys Met Ala Gln Ala Gln His Leu Gly
6820 6825 6830

Lys Leu Val Leu Ala Leu Glu Asp Pro Asp Val Arg Ile Arg Val Pro
6835 6840 6845

Gly Glu Ser Gly Val Ala Ile Arg Ala Asp Gly Ala Tyr Leu Val Thr
6850 6855 6860

Gly Gly Leu Gly Gly Leu Gly Leu Ser Val Ala Gly Trp Leu Ala Glu
6865 6870 6875 6880

Gln Gly Ala Gly His Leu Val Leu Val Gly Arg Ser Gly Ala Val Ser
6885 6890 6895

Ala Glu Gln Gln Thr Ala Val Ala Ala Leu Glu Ala His Gly Ala Arg
6900 6905 6910

Val Thr Val Ala Arg Ala Asp Val Ala Asp Arg Ala Gln Met Glu Arg
6915 6920 6925

Ile Leu Arg Glu Val Thr Ala Ser Gly Met Pro Leu Arg Gly Val Val
6930 6935 6940

His Ala Ala Gly Ile Leu Asp Asp Gly Leu Leu Met Gln Gln Thr Pro
6945 6950 6955 6960

Ala Arg Phe Arg Ala Val Met Ala Pro Lys Val Arg Gly Ala Leu His

6965 6970 6975

Leu His Ala Leu Thr Arg Glu Ala Pro Leu Ser Phe Phe Val Leu Tyr
6980 6985 6990

Ala Ser Gly Ala Gly Leu Leu Gly Ser Pro Gly Gln Gly Asn Tyr Ala
6995 7000 7005

Ala Ala Asn Thr Phe Leu Asp Ala Leu Ala His His Arg Arg Ala Gln
7010 7015 7020

Gly Leu Pro Ala Leu Ser Ile Asp Trp Gly Leu Phe Ala Asp Val Gly
7025 7030 7035 7040

Leu Ala Ala Gly Gln Gln Asn Arg Gly Ala Arg Leu Val Thr Arg Gly
7045 7050 7055

Thr Arg Ser Leu Thr Pro Asp Glu Gly Leu Trp Ala Leu Glu Arg Leu
7060 7065 7070

Leu Asp Gly Asp Arg Thr Gln Ala Gly Val Met Pro Phe Asp Val Arg
7075 7080 7085

Gln Trp Val Glu Phe Tyr Pro Ala Ala Ala Ser Ser Arg Arg Leu Ser
7090 7095 7100

Arg Leu Met Thr Ala Arg Arg Val Ala Ser Gly Arg Leu Ala Gly Asp
7105 7110 7115 7120

Arg Asp Leu Leu Glu Arg Leu Ala Thr Ala Glu Ala Gly Ala Arg Ala
7125 7130 7135

Gly Met Leu Gln Glu Val Val Arg Ala Gln Val Ser Gln Val Leu Arg
7140 7145 7150

Leu Ser Glu Gly Lys Leu Asp Val Asp Ala Pro Leu Thr Ser Leu Gly
7155 7160 7165

Met Asp Ser Leu Met Gly Leu Glu Leu Arg Asn Arg Ile Glu Ala Val
7170 7175 7180

Leu Gly Ile Thr Met Pro Ala Thr Leu Leu Trp Thr Tyr Pro Thr Val
7185 7190 7195 7200

Ala Ala Leu Ser Ala His Leu Ala Ser His Val Val Ser Thr Gly Asp
7205 7210 7215

Gly Glu Ser Ala Arg Pro Pro Asp Thr Gly Ser Val Ala Pro Thr Thr
7220 7225 7230

His Glu Val Ala Ser Leu Asp Glu Asp Gly Leu Phe Ala Leu Ile Asp
7235 7240 7245

Glu Ser Leu Ala Arg Ala Gly Lys Arg
7250 7255

<210> 6
<211> 3798
<212> PRT
<213> Sorangium cellulosum

<400> 6
Val Thr Asp Arg Glu Gly Gln Leu Leu Glu Arg Leu Arg Glu Val Thr
1 5 10 15

```
Leu Ala Leu Arg Lys Thr Leu Asn Glu Arg Asp Thr Leu Glu Leu Glu
            20                  25                  30

Lys Thr Glu Pro Ile Ala Ile Val Gly Ile Gly Cys Arg Phe Pro Gly
        35                  40                  45

Gly Ala Gly Thr Pro Glu Ala Phe Trp Glu Leu Leu Asp Asp Gly Arg
    50                  55                  60

Asp Ala Ile Arg Pro Leu Glu Glu Arg Trp Ala Leu Val Gly Val Asp
65                  70                  75                  80

Pro Gly Asp Asp Val Pro Arg Trp Ala Gly Leu Leu Thr Glu Ala Ile
                85                  90                  95

Asp Gly Phe Asp Ala Ala Phe Phe Gly Ile Ala Pro Arg Glu Ala Arg
            100                 105                 110

Ser Leu Asp Pro Gln His Arg Leu Leu Leu Glu Val Ala Trp Glu Gly
        115                 120                 125

Phe Glu Asp Ala Gly Ile Pro Pro Arg Ser Leu Val Gly Ser Arg Thr
    130                 135                 140

Gly Val Phe Val Gly Val Cys Ala Thr Glu Tyr Leu His Ala Ala Val
145                 150                 155                 160

Ala His Gln Pro Arg Glu Glu Arg Asp Ala Tyr Ser Thr Thr Gly Asn
                165                 170                 175

Met Leu Ser Ile Ala Ala Gly Arg Leu Ser Tyr Thr Leu Gly Leu Gln
            180                 185                 190

Gly Pro Cys Leu Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala
        195                 200                 205

Ile His Leu Ala Cys Arg Ser Leu Arg Ala Arg Glu Ser Asp Leu Ala
    210                 215                 220

Leu Ala Gly Gly Val Asn Met Leu Leu Ser Pro Asp Thr Met Arg Ala
225                 230                 235                 240

Leu Ala Arg Thr Gln Ala Leu Ser Pro Asn Gly Arg Cys Gln Thr Phe
                245                 250                 255

Asp Ala Ser Ala Asn Gly Phe Val Arg Gly Glu Gly Cys Gly Leu Ile
            260                 265                 270

Val Leu Lys Arg Leu Ser Asp Ala Arg Arg Asp Gly Asp Arg Ile Trp
        275                 280                 285

Ala Leu Ile Arg Gly Ser Ala Ile Asn Gln Asp Gly Arg Ser Thr Gly
    290                 295                 300

Leu Thr Ala Pro Asn Val Leu Ala Gln Gly Ala Leu Leu Arg Glu Ala
305                 310                 315                 320

Leu Arg Asn Ala Gly Val Glu Ala Glu Ala Ile Gly Tyr Ile Glu Thr
                325                 330                 335

His Gly Ala Ala Thr Ser Leu Gly Asp Pro Ile Glu Ile Glu Ala Leu
            340                 345                 350

Arg Ala Val Val Gly Pro Ala Arg Ala Asp Gly Ala Arg Cys Val Leu
```

355 360 365

Gly Ala Val Lys Thr Asn Leu Gly His Leu Glu Gly Ala Ala Gly Val
370 375 380

Ala Gly Leu Ile Lys Ala Thr Leu Ser Leu His His Glu Arg Ile Pro
385 390 395 400

Arg Asn Leu Asn Phe Arg Thr Leu Asn Pro Arg Ile Arg Ile Glu Gly
405 410 415

Thr Ala Leu Ala Leu Ala Thr Glu Pro Val Pro Trp Pro Arg Thr Gly
420 425 430

Arg Thr Arg Phe Ala Gly Val Ser Ser Phe Gly Met Ser Gly Thr Asn
435 440 445

Ala His Val Val Leu Glu Glu Ala Pro Ala Val Glu Pro Glu Ala Ala
450 455 460

Ala Pro Glu Arg Ala Ala Glu Leu Phe Val Leu Ser Ala Lys Ser Ala
465 470 475 480

Ala Ala Leu Asp Ala Gln Ala Ala Arg Leu Arg Asp His Leu Glu Lys
485 490 495

His Val Glu Leu Gly Leu Gly Asp Val Ala Phe Ser Leu Ala Thr Thr
500 505 510

Arg Ser Ala Met Glu His Arg Leu Ala Val Ala Ala Ser Ser Arg Glu
515 520 525

Ala Leu Arg Gly Ala Leu Ser Ala Ala Ala Gln Gly His Thr Pro Pro
530 535 540

Gly Ala Val Arg Gly Arg Ala Ser Gly Gly Ser Ala Pro Lys Val Val
545 550 555 560

Phe Val Phe Pro Gly Gln Gly Ser Gln Trp Val Gly Met Gly Arg Lys
565 570 575

Leu Met Ala Glu Glu Pro Val Phe Arg Ala Ala Leu Glu Gly Cys Asp
580 585 590

Arg Ala Ile Glu Ala Glu Ala Gly Trp Ser Leu Leu Gly Glu Leu Ser
595 600 605

Ala Asp Glu Ala Ala Ser Gln Leu Gly Arg Ile Asp Val Val Gln Pro
610 615 620

Val Leu Phe Ala Met Glu Val Ala Leu Ser Ala Leu Trp Arg Ser Trp
625 630 635 640

Gly Val Glu Pro Glu Ala Val Val Gly His Ser Met Gly Glu Val Ala
645 650 655

Ala Ala His Val Ala Gly Ala Leu Ser Leu Glu Asp Ala Val Ala Ile
660 665 670

Ile Cys Arg Arg Ser Arg Leu Leu Arg Arg Ile Ser Gly Gln Gly Glu
675 680 685

Met Ala Leu Val Glu Leu Ser Leu Glu Glu Ala Glu Ala Ala Leu Arg
690 695 700

Gly His Glu Gly Arg Leu Ser Val Ala Val Ser Asn Ser Pro Arg Ser
705 710 715 720

Thr Val Leu Ala Gly Glu Pro Ala Ala Leu Ser Glu Val Leu Ala Ala
725 730 735

Leu Thr Ala Lys Gly Val Phe Trp Arg Gln Val Lys Val Asp Val Ala
740 745 750

Ser His Ser Pro Gln Val Asp Pro Leu Arg Glu Glu Leu Ile Ala Ala
755 760 765

Leu Gly Ala Ile Arg Pro Arg Ala Ala Ala Val Pro Met Arg Ser Thr
770 775 780

Val Thr Gly Gly Val Ile Ala Gly Pro Glu Leu Gly Ala Ser Tyr Trp
785 790 795 800

Ala Asp Asn Leu Arg Gln Pro Val Arg Phe Ala Ala Ala Ala Gln Ala
805 810 815

Leu Leu Glu Gly Gly Pro Ala Leu Phe Ile Glu Met Ser Pro His Pro
820 825 830

Ile Leu Val Pro Pro Leu Asp Glu Ile Gln Thr Ala Ala Glu Gln Gly
835 840 845

Gly Ala Ala Val Gly Ser Leu Arg Arg Gly Gln Asp Glu Arg Ala Thr
850 855 860

Leu Leu Glu Ala Leu Gly Thr Leu Trp Ala Ser Gly Tyr Pro Val Ser
865 870 875 880

Trp Ala Arg Leu Phe Pro Ala Gly Gly Arg Arg Val Pro Leu Pro Thr
885 890 895

Tyr Pro Trp Gln His Glu Arg Cys Trp Ile Glu Val Glu Pro Asp Ala
900 905 910

Arg Arg Leu Ala Ala Ala Asp Pro Thr Lys Asp Trp Phe Tyr Arg Thr
915 920 925

Asp Trp Pro Glu Val Pro Arg Ala Ala Pro Lys Ser Glu Thr Ala His
930 935 940

Gly Ser Trp Leu Leu Leu Ala Asp Arg Gly Gly Val Gly Glu Ala Val
945 950 955 960

Ala Ala Ala Leu Ser Thr Arg Gly Leu Ser Cys Thr Val Leu His Ala
965 970 975

Ser Ala Asp Ala Ser Thr Val Ala Glu Gln Val Ser Glu Ala Ala Ser
980 985 990

Arg Arg Asn Asp Trp Gln Gly Val Leu Tyr Leu Trp Gly Leu Asp Ala
995 1000 1005

Val Val Asp Ala Gly Ala Ser Ala Asp Glu Val Ser Glu Ala Thr Arg
1010 1015 1020

Arg Ala Thr Ala Pro Val Leu Gly Leu Val Arg Phe Leu Ser Ala Ala
1025 1030 1035 1040

Pro His Pro Pro Arg Phe Trp Val Val Thr Arg Gly Ala Cys Thr Val
1045 1050 1055

Gly Gly Glu Pro Glu Ala Ser Leu Cys Gln Ala Ala Leu Trp Gly Leu
1060 1065 1070

Ala Arg Val Ala Ala Leu Glu His Pro Ala Ala Trp Gly Gly Leu Val
1075 1080 1085

Asp Leu Asp Pro Gln Lys Ser Pro Thr Glu Ile Glu Pro Leu Val Ala
1090 1095 1100

Glu Leu Leu Ser Pro Asp Ala Glu Asp Gln Leu Ala Phe Arg Ser Gly
1105 1110 1115 1120

Arg Arg His Ala Ala Arg Leu Val Ala Ala Pro Pro Glu Gly Asp Val
1125 1130 1135

Ala Pro Ile Ser Leu Ser Ala Glu Gly Ser Tyr Leu Val Thr Gly Gly
1140 1145 1150

Leu Gly Gly Leu Gly Leu Leu Val Ala Arg Trp Leu Val Glu Arg Gly
1155 1160 1165

Ala Arg His Leu Val Leu Thr Ser Arg His Gly Leu Pro Glu Arg Gln
1170 1175 1180

Ala Ser Gly Gly Glu Gln Pro Pro Glu Ala Arg Ala Arg Ile Ala Ala
1185 1190 1195 1200

Val Glu Gly Leu Glu Ala Gln Gly Ala Arg Val Thr Val Ala Ala Val
1205 1210 1215

Asp Val Ala Glu Ala Asp Pro Met Thr Ala Leu Leu Ala Ala Ile Glu
1220 1225 1230

Pro Pro Leu Arg Gly Val Val His Ala Ala Gly Val Phe Pro Val Arg
1235 1240 1245

His Leu Ala Glu Thr Asp Glu Ala Leu Leu Glu Ser Val Leu Arg Pro
1250 1255 1260

Lys Val Ala Gly Ser Trp Leu Leu His Arg Leu Leu Arg Asp Arg Pro
1265 1270 1275 1280

Leu Asp Leu Phe Val Leu Phe Ser Ser Gly Ala Ala Val Trp Gly Gly
1285 1290 1295

Lys Gly Gln Gly Ala Tyr Ala Ala Ala Asn Ala Phe Leu Asp Gly Leu
1300 1305 1310

Ala His His Arg Arg Ala His Ser Leu Pro Ala Leu Ser Leu Ala Trp
1315 1320 1325

Gly Leu Trp Ala Glu Gly Gly Met Val Asp Ala Lys Ala His Ala Arg
1330 1335 1340

Leu Ser Asp Ile Gly Val Leu Pro Met Ala Thr Gly Pro Ala Leu Ser
1345 1350 1355 1360

Ala Leu Glu Arg Leu Val Asn Thr Ser Ala Val Gln Arg Ser Val Thr
1365 1370 1375

Arg Met Asp Trp Ala Arg Phe Ala Pro Val Tyr Ala Ala Arg Gly Arg
1380 1385 1390

Arg Asn Leu Leu Ser Ala Leu Val Ala Glu Asp Glu Arg Ala Ala Ser

1395 1400 1405

Pro Pro Val Pro Thr Ala Asn Arg Ile Trp Arg Gly Leu Ser Val Ala
1410 1415 1420

Glu Ser Arg Ser Ala Leu Tyr Glu Leu Val Arg Gly Ile Val Ala Arg
1425 1430 1435 1440

Val Leu Gly Phe Ser Asp Pro Gly Ala Leu Asp Val Gly Arg Gly Phe
1445 1450 1455

Ala Glu Gln Gly Leu Asp Ser Leu Met Ala Leu Glu Ile Arg Asn Arg
1460 1465 1470

Leu Gln Arg Glu Leu Gly Glu Arg Leu Ser Ala Thr Leu Ala Phe Asp
1475 1480 1485

His Pro Thr Val Glu Arg Leu Val Ala His Leu Leu Thr Asp Val Leu
1490 1495 1500

Lys Leu Glu Asp Arg Ser Asp Thr Arg His Ile Arg Ser Val Ala Ala
1505 1510 1515 1520

Asp Asp Asp Ile Ala Ile Val Gly Ala Ala Cys Arg Phe Pro Gly Gly
1525 1530 1535

Asp Glu Gly Leu Glu Thr Tyr Trp Arg His Leu Ala Glu Gly Met Val
1540 1545 1550

Val Ser Thr Glu Val Pro Ala Asp Arg Trp Arg Ala Ala Asp Trp Tyr
1555 1560 1565

Asp Pro Asp Pro Glu Val Pro Gly Arg Thr Tyr Val Ala Lys Gly Ala
1570 1575 1580

Phe Leu Arg Asp Val Arg Ser Leu Asp Ala Ala Phe Phe Ala Ile Ser
1585 1590 1595 1600

Pro Arg Glu Ala Met Ser Leu Asp Pro Gln Gln Arg Leu Leu Leu Glu
1605 1610 1615

Val Ser Trp Glu Ala Ile Glu Arg Ala Gly Gln Asp Pro Met Ala Leu
1620 1625 1630

Arg Glu Ser Ala Thr Gly Val Phe Val Gly Met Ile Gly Ser Glu His
1635 1640 1645

Ala Glu Arg Val Gln Gly Leu Asp Asp Asp Ala Ala Leu Leu Tyr Gly
1650 1655 1660

Thr Thr Gly Asn Leu Leu Ser Val Ala Ala Gly Arg Leu Ser Phe Phe
1665 1670 1675 1680

Leu Gly Leu His Gly Pro Thr Met Thr Val Asp Thr Ala Cys Ser Ser
1685 1690 1695

Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Leu Gly Glu
1700 1705 1710

Cys Asp Gln Ala Leu Ala Gly Gly Ser Ser Val Leu Leu Ser Pro Arg
1715 1720 1725

Ser Phe Val Ala Ala Ser Arg Met Arg Leu Leu Ser Pro Asp Gly Arg
1730 1735 1740

Cys Lys Thr Phe Ser Ala Ala Ala Asp Gly Phe Ala Arg Ala Glu Gly
1745 1750 1755 1760

Cys Ala Val Val Val Leu Lys Arg Leu Arg Asp Ala Gln Arg Asp Arg
1765 1770 1775

Asp Pro Ile Leu Ala Val Val Arg Ser Thr Ala Ile Asn His Asp Gly
1780 1785 1790

Pro Ser Ser Gly Leu Thr Val Pro Ser Gly Pro Ala Gln Gln Ala Leu
1795 1800 1805

Leu Arg Gln Ala Leu Ala Gln Ala Gly Val Ala Pro Ala Glu Val Asp
1810 1815 1820

Phe Val Glu Cys His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu
1825 1830 1835 1840

Val Gln Ala Leu Gly Ala Val Tyr Gly Arg Gly Arg Pro Ala Glu Arg
1845 1850 1855

Pro Leu Trp Leu Gly Ala Val Lys Ala Asn Leu Gly His Leu Glu Ala
1860 1865 1870

Ala Ala Gly Leu Ala Gly Val Leu Lys Val Leu Leu Ala Leu Glu His
1875 1880 1885

Glu Gln Ile Pro Ala Gln Pro Glu Leu Asp Glu Leu Asn Pro His Ile
1890 1895 1900

Pro Trp Ala Glu Leu Pro Val Ala Val Val Arg Arg Ala Val Pro Trp
1905 1910 1915 1920

Pro Arg Gly Ala Arg Pro Arg Arg Ala Gly Val Ser Ala Phe Gly Leu
1925 1930 1935

Ser Gly Thr Asn Ala His Val Val Leu Glu Glu Ala Pro Ala Val Glu
1940 1945 1950

Pro Val Ala Ala Ala Pro Glu Arg Ala Ala Glu Leu Phe Val Leu Ser
1955 1960 1965

Ala Lys Ser Ala Ala Ala Leu Asp Ala Gln Ala Ala Arg Leu Arg Asp
1970 1975 1980

His Leu Glu Lys His Val Glu Leu Gly Leu Gly Asp Val Ala Phe Ser
1985 1990 1995 2000

Leu Ala Thr Thr Arg Ser Ala Met Glu His Arg Leu Ala Val Ala Ala
2005 2010 2015

Ser Ser Arg Glu Ala Leu Arg Gly Ala Leu Ser Ala Ala Ala Gln Gly
2020 2025 2030

His Thr Pro Pro Gly Ala Val Arg Gly Arg Ala Ser Gly Gly Ser Ala
2035 2040 2045

Pro Lys Val Val Phe Val Phe Pro Gly Gln Gly Ser Gln Trp Val Gly
2050 2055 2060

Met Gly Arg Lys Leu Met Ala Glu Glu Pro Val Phe Arg Ala Ala Leu
2065 2070 2075 2080

Glu Gly Cys Asp Arg Ala Ile Glu Ala Glu Ala Gly Trp Ser Leu Leu
2085 2090 2095

Gly Glu Leu Ser Ala Asp Glu Ala Ala Ser Gln Leu Gly Arg Ile Asp
2100 2105 2110

Val Val Gln Pro Val Leu Phe Ala Met Glu Val Ala Leu Ser Ala Leu
2115 2120 2125

Trp Arg Ser Trp Gly Val Glu Pro Glu Ala Val Val Gly His Ser Met
2130 2135 2140

Gly Glu Val Ala Ala Ala His Val Ala Gly Ala Leu Ser Leu Glu Asp
2145 2150 2155 2160

Ala Val Ala Ile Ile Cys Arg Arg Ser Arg Leu Leu Arg Arg Ile Ser
2165 2170 2175

Gly Gln Gly Glu Met Ala Leu Val Glu Leu Ser Leu Glu Glu Ala Glu
2180 2185 2190

Ala Ala Leu Arg Gly His Glu Gly Arg Leu Ser Val Ala Val Ser Asn
2195 2200 2205

Ser Pro Arg Ser Thr Val Leu Ala Gly Glu Pro Ala Ala Leu Ser Glu
2210 2215 2220

Val Leu Ala Ala Leu Thr Ala Lys Gly Val Phe Trp Arg Gln Val Lys
2225 2230 2235 2240

Val Asp Val Ala Ser His Ser Pro Gln Val Asp Pro Leu Arg Glu Glu
2245 2250 2255

Leu Ile Ala Ala Leu Gly Ala Ile Arg Pro Arg Ala Ala Ala Val Pro
2260 2265 2270

Met Arg Ser Thr Val Thr Gly Gly Val Ile Ala Gly Pro Glu Leu Gly
2275 2280 2285

Ala Ser Tyr Trp Ala Asp Asn Leu Arg Gln Pro Val Arg Phe Ala Ala
2290 2295 2300

Ala Ala Gln Ala Leu Leu Glu Gly Gly Pro Ala Leu Phe Ile Glu Met
2305 2310 2315 2320

Ser Pro His Pro Ile Leu Val Pro Pro Leu Asp Glu Ile Gln Thr Ala
2325 2330 2335

Ala Glu Gln Gly Gly Ala Ala Val Gly Ser Leu Arg Arg Gly Gln Asp
2340 2345 2350

Glu Arg Ala Thr Leu Leu Glu Ala Leu Gly Thr Leu Trp Ala Ser Gly
2355 2360 2365

Tyr Pro Val Ser Trp Ala Arg Leu Phe Pro Ala Gly Gly Arg Arg Val
2370 2375 2380

Pro Leu Pro Thr Tyr Pro Trp Gln His Glu Arg Tyr Trp Ile Glu Asp
2385 2390 2395 2400

Ser Val His Gly Ser Lys Pro Ser Leu Arg Leu Arg Gln Leu Arg Asn
2405 2410 2415

Gly Ala Thr Asp His Pro Leu Leu Gly Ala Pro Leu Leu Val Ser Ala
2420 2425 2430

Arg Pro Gly Ala His Leu Trp Glu Gln Ala Leu Ser Asp Glu Arg Leu

2435 2440 2445

Ser Tyr Leu Ser Glu His Arg Val His Gly Glu Ala Val Leu Pro Ser
2450 2455 2460

Ala Ala Tyr Val Glu Met Ala Leu Ala Ala Gly Val Asp Leu Tyr Gly
2465 2470 2475 2480

Thr Ala Thr Leu Val Leu Glu Gln Leu Ala Leu Glu Arg Ala Leu Ala
2485 2490 2495

Val Pro Ser Glu Gly Gly Arg Ile Val Gln Val Ala Leu Ser Glu Glu
2500 2505 2510

Gly Pro Gly Arg Ala Ser Phe Gln Val Ser Ser Arg Glu Glu Ala Gly
2515 2520 2525

Arg Ser Trp Val Arg His Ala Thr Gly His Val Cys Ser Gly Gln Ser
2530 2535 2540

Ser Ala Val Gly Ala Leu Lys Glu Ala Pro Trp Glu Ile Gln Arg Arg
2545 2550 2555 2560

Cys Pro Ser Val Leu Ser Ser Glu Ala Leu Tyr Pro Leu Leu Asn Glu
2565 2570 2575

His Ala Leu Asp Tyr Gly Pro Cys Phe Gln Gly Val Glu Gln Val Trp
2580 2585 2590

Leu Gly Thr Gly Glu Val Leu Gly Arg Val Arg Leu Pro Gly Asp Met
2595 2600 2605

Ala Ser Ser Ser Gly Ala Tyr Arg Ile His Pro Ala Leu Leu Asp Ala
2610 2615 2620

Cys Phe Gln Val Leu Thr Ala Leu Leu Thr Thr Pro Glu Ser Ile Glu
2625 2630 2635 2640

Ile Arg Arg Arg Leu Thr Asp Leu His Glu Pro Asp Leu Pro Arg Ser
2645 2650 2655

Arg Ala Pro Val Asn Gln Ala Val Ser Asp Thr Trp Leu Trp Asp Ala
2660 2665 2670

Ala Leu Asp Gly Gly Arg Arg Gln Ser Ala Ser Val Pro Val Asp Leu
2675 2680 2685

Val Leu Gly Ser Phe His Ala Lys Trp Glu Val Met Glu Arg Leu Ala
2690 2695 2700

Gln Ala Tyr Ile Ile Gly Thr Leu Arg Ile Trp Asn Val Phe Cys Ala
2705 2710 2715 2720

Ala Gly Glu Arg His Thr Ile Asp Glu Leu Leu Val Arg Leu Gln Ile
2725 2730 2735

Ser Val Val Tyr Arg Lys Val Ile Lys Arg Trp Met Glu His Leu Val
2740 2745 2750

Ala Ile Gly Ile Leu Val Gly Asp Gly Glu His Phe Val Ser Ser Gln
2755 2760 2765

Pro Leu Pro Glu Pro Asp Leu Ala Ala Val Leu Glu Glu Ala Gly Arg
2770 2775 2780

```
Val Phe Ala Asp Leu Pro Val Leu Phe Glu Trp Cys Lys Phe Ala Gly
2785                2790                2795                2800

Glu Arg Leu Ala Asp Val Leu Thr Gly Lys Thr Leu Ala Leu Glu Ile
                2805                2810                2815

Leu Phe Pro Gly Gly Ser Phe Asp Met Ala Glu Arg Ile Tyr Arg Asp
            2820                2825                2830

Ser Pro Ile Ala Arg Tyr Ser Asn Gly Ile Val Arg Gly Val Val Glu
        2835                2840                2845

Ser Ala Ala Arg Val Val Ala Pro Ser Gly Met Phe Ser Ile Leu Glu
    2850                2855                2860

Ile Gly Ala Gly Thr Gly Ala Thr Thr Ala Ala Val Leu Pro Val Leu
2865                2870                2875                2880

Leu Pro Asp Arg Thr Glu Tyr His Phe Thr Asp Val Ser Pro Leu Phe
                2885                2890                2895

Leu Ala Arg Ala Glu Gln Arg Phe Arg Asp Tyr Pro Phe Leu Lys Tyr
            2900                2905                2910

Gly Ile Leu Asp Val Asp Gln Glu Pro Ala Gly Gln Gly Tyr Ala His
        2915                2920                2925

Gln Arg Phe Asp Val Ile Val Ala Ala Asn Val Ile His Ala Thr Arg
    2930                2935                2940

Asp Ile Arg Ala Thr Ala Lys Arg Leu Leu Ser Leu Leu Ala Pro Gly
2945                2950                2955                2960

Gly Leu Leu Val Leu Val Glu Gly Thr Gly His Pro Ile Trp Phe Asp
                2965                2970                2975

Ile Thr Thr Gly Leu Ile Glu Gly Trp Gln Lys Tyr Glu Asp Asp Leu
            2980                2985                2990

Arg Ile Asp His Pro Leu Leu Pro Ala Arg Thr Trp Cys Asp Val Leu
        2995                3000                3005

Arg Arg Val Gly Phe Ala Asp Ala Val Ser Leu Pro Gly Asp Gly Ser
    3010                3015                3020

Pro Ala Gly Ile Leu Gly Gln His Val Ile Leu Ser Arg Ala Pro Gly
3025                3030                3035                3040

Ile Ala Gly Ala Ala Cys Asp Ser Ser Gly Glu Ser Ala Thr Glu Ser
                3045                3050                3055

Pro Ala Ala Arg Ala Val Arg Gln Glu Trp Ala Asp Gly Ser Ala Asp
            3060                3065                3070

Val Val His Arg Met Ala Leu Glu Arg Met Tyr Phe His Arg Arg Pro
        3075                3080                3085

Gly Arg Gln Val Trp Val His Gly Arg Leu Arg Thr Gly Gly Gly Ala
    3090                3095                3100

Phe Thr Lys Ala Leu Ala Gly Asp Leu Leu Leu Phe Glu Asp Thr Gly
3105                3110                3115                3120

Gln Val Val Ala Glu Val Gln Gly Leu Arg Leu Pro Gln Leu Glu Ala
                3125                3130                3135
```

```
Ser Ala Phe Ala Pro Arg Asp Pro Arg Glu Glu Trp Leu Tyr Ala Leu
            3140                3145                3150

Glu Trp Gln Arg Lys Asp Pro Ile Pro Glu Ala Pro Ala Ala Ala Ser
        3155                3160                3165

Ser Ser Ser Ala Gly Ala Trp Leu Val Leu Met Asp Gln Gly Gly Thr
    3170                3175                3180

Gly Ala Ala Leu Val Ser Leu Leu Glu Gly Arg Gly Glu Ala Cys Val
3185                3190                3195                3200

Arg Val Ile Ala Gly Thr Ala Tyr Ala Cys Leu Ala Pro Gly Leu Tyr
                3205                3210                3215

Gln Val Asp Pro Ala Gln Pro Asp Gly Phe His Thr Leu Leu Arg Asp
            3220                3225                3230

Ala Phe Gly Glu Asp Arg Ile Cys Arg Ala Val Val His Met Trp Ser
        3235                3240                3245

Leu Asp Ala Thr Ala Ala Gly Glu Arg Ala Thr Ala Glu Ser Leu Gln
    3250                3255                3260

Ala Asp Gln Leu Leu Gly Ser Leu Ser Ala Leu Ser Leu Val Gln Ala
3265                3270                3275                3280

Leu Val Arg Arg Arg Trp Arg Asn Met Pro Arg Leu Trp Leu Leu Thr
                3285                3290                3295

Arg Ala Val His Ala Val Gly Ala Glu Asp Ala Ala Ala Ser Val Ala
            3300                3305                3310

Gln Ala Pro Val Trp Gly Leu Gly Arg Thr Leu Ala Leu Glu His Pro
        3315                3320                3325

Glu Leu Arg Cys Thr Leu Val Asp Val Asn Pro Ala Pro Ser Pro Glu
    3330                3335                3340

Asp Ala Ala Ala Leu Ala Val Glu Leu Gly Ala Ser Asp Arg Glu Asp
3345                3350                3355                3360

Gln Val Ala Leu Arg Ser Asp Gly Arg Tyr Val Ala Arg Leu Val Arg
                3365                3370                3375

Ser Ser Phe Ser Gly Lys Pro Ala Thr Asp Cys Gly Ile Arg Ala Asp
            3380                3385                3390

Gly Ser Tyr Val Ile Thr Asp Gly Met Gly Arg Val Gly Leu Ser Val
        3395                3400                3405

Ala Gln Trp Met Val Met Gln Gly Ala Arg His Val Val Leu Val Asp
    3410                3415                3420

Arg Gly Gly Ala Ser Glu Ala Ser Arg Asp Ala Leu Arg Ser Met Ala
3425                3430                3435                3440

Glu Ala Gly Ala Glu Val Gln Ile Val Glu Ala Asp Val Ala Arg Arg
                3445                3450                3455

Asp Asp Val Ala Arg Leu Leu Ser Lys Ile Glu Pro Ser Met Pro Pro
            3460                3465                3470

Leu Arg Gly Ile Val Tyr Val Asp Gly Thr Phe Gln Gly Asp Ser Ser
```

3475 3480 3485

Met Leu Glu Leu Asp Ala Arg Arg Phe Lys Glu Trp Met Tyr Pro Lys
3490 3495 3500

Val Leu Gly Ala Trp Asn Leu His Ala Leu Thr Arg Asp Arg Ser Leu
3505 3510 3515 3520

Asp Phe Phe Val Leu Tyr Ser Ser Gly Thr Ser Leu Leu Gly Leu Pro
3525 3530 3535

Gly Gln Gly Ser Arg Ala Ala Gly Asp Ala Phe Leu Asp Ala Ile Ala
3540 3545 3550

His His Arg Cys Lys Val Gly Leu Thr Ala Met Ser Ile Asn Trp Gly
3555 3560 3565

Leu Leu Ser Glu Ala Ser Ser Pro Ala Thr Pro Asn Asp Gly Gly Ala
3570 3575 3580

Arg Leu Glu Tyr Arg Gly Met Glu Gly Leu Thr Leu Glu Gln Gly Ala
3585 3590 3595 3600

Ala Ala Leu Gly Arg Leu Leu Ala Arg Pro Arg Ala Gln Val Gly Val
3605 3610 3615

Met Arg Leu Asn Leu Arg Gln Trp Leu Glu Phe Tyr Pro Asn Ala Ala
3620 3625 3630

Arg Leu Ala Leu Trp Ala Glu Leu Leu Lys Glu Arg Asp Arg Ala Asp
3635 3640 3645

Arg Gly Ala Ser Asn Ala Ser Asn Leu Arg Glu Ala Leu Gln Ser Ala
3650 3655 3660

Arg Pro Glu Asp Arg Gln Leu Ile Leu Glu Lys His Leu Ser Glu Leu
3665 3670 3675 3680

Leu Gly Arg Gly Leu Arg Leu Pro Pro Glu Arg Ile Glu Arg His Val
3685 3690 3695

Pro Phe Ser Asn Leu Gly Met Asp Ser Leu Ile Gly Leu Glu Leu Arg
3700 3705 3710

Asn Arg Ile Glu Ala Ala Leu Gly Ile Thr Val Pro Ala Thr Leu Leu
3715 3720 3725

Trp Thr Tyr Pro Asn Val Ala Ala Leu Ser Gly Ser Leu Leu Asp Ile
3730 3735 3740

Leu Phe Pro Asn Ala Gly Ala Thr His Ala Pro Ala Thr Glu Arg Glu
3745 3750 3755 3760

Lys Ser Phe Glu Asn Asp Ala Ala Asp Leu Glu Ala Leu Arg Gly Met
3765 3770 3775

Thr Asp Glu Gln Lys Asp Ala Leu Leu Ala Glu Lys Leu Ala Gln Leu
3780 3785 3790

Ala Gln Ile Val Gly Glu
3795

<210> 7
<211> 2439

<212> PRT
<213> Sorangium cellulosum

<400> 7
Met Ala Thr Thr Asn Ala Gly Lys Leu Glu His Ala Leu Leu Leu Met
1 5 10 15

Asp Lys Leu Ala Lys Lys Asn Ala Ser Leu Glu Gln Glu Arg Thr Glu
20 25 30

Pro Ile Ala Ile Val Gly Ile Gly Cys Arg Phe Pro Gly Gly Ala Asp
35 40 45

Thr Pro Glu Ala Phe Trp Glu Leu Leu Asp Ser Gly Arg Asp Ala Val
50 55 60

Gln Pro Leu Asp Arg Arg Trp Ala Leu Val Gly Val His Pro Ser Glu
65 70 75 80

Glu Val Pro Arg Trp Ala Gly Leu Leu Thr Glu Ala Val Asp Gly Phe
85 90 95

Asp Ala Ala Phe Phe Gly Thr Ser Pro Arg Glu Ala Arg Ser Leu Asp
100 105 110

Pro Gln Gln Arg Leu Leu Leu Glu Val Thr Trp Glu Gly Leu Glu Asp
115 120 125

Ala Gly Ile Ala Pro Gln Ser Leu Asp Gly Ser Arg Thr Gly Val Phe
130 135 140

Leu Gly Ala Cys Ser Ser Asp Tyr Ser His Thr Val Ala Gln Gln Arg
145 150 155 160

Arg Glu Glu Gln Asp Ala Tyr Asp Ile Thr Gly Asn Thr Leu Ser Val
165 170 175

Ala Ala Gly Arg Leu Ser Tyr Thr Leu Gly Leu Gln Gly Pro Cys Leu
180 185 190

Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Ile His Leu Ala
195 200 205

Cys Arg Ser Leu Arg Ala Arg Glu Ser Asp Leu Ala Leu Ala Gly Gly
210 215 220

Val Asn Met Leu Leu Ser Ser Lys Thr Met Ile Met Leu Gly Arg Ile
225 230 235 240

Gln Ala Leu Ser Pro Asp Gly His Cys Arg Thr Phe Asp Ala Ser Ala
245 250 255

Asn Gly Phe Val Arg Gly Glu Gly Cys Gly Met Val Val Leu Lys Arg
260 265 270

Leu Ser Asp Ala Gln Arg His Gly Asp Arg Ile Trp Ala Leu Ile Arg
275 280 285

Gly Ser Ala Met Asn Gln Asp Gly Arg Ser Thr Gly Leu Met Ala Pro
290 295 300

Asn Val Leu Ala Gln Glu Ala Leu Leu Arg Glu Ala Leu Gln Ser Ala
305 310 315 320

Arg Val Asp Ala Gly Ala Ile Gly Tyr Val Glu Thr His Gly Thr Gly

325 330 335

Thr Ser Leu Gly Asp Pro Ile Glu Val Glu Ala Leu Arg Ala Val Leu
340 345 350

Gly Pro Ala Arg Ala Asp Gly Ser Arg Cys Val Leu Gly Ala Val Lys
355 360 365

Thr Asn Leu Gly His Leu Glu Gly Ala Ala Gly Val Ala Gly Leu Ile
370 375 380

Lys Ala Ala Leu Ala Leu His His Glu Leu Ile Pro Arg Asn Leu His
385 390 395 400

Phe His Thr Leu Asn Pro Arg Ile Arg Ile Glu Gly Thr Ala Leu Ala
405 410 415

Leu Ala Thr Glu Pro Val Pro Trp Pro Arg Ala Gly Arg Pro Arg Phe
420 425 430

Ala Gly Val Ser Ala Phe Gly Leu Ser Gly Thr Asn Val His Val Val
435 440 445

Leu Glu Glu Ala Pro Ala Thr Val Leu Ala Pro Ala Thr Pro Gly Arg
450 455 460

Ser Ala Glu Leu Leu Val Leu Ser Ala Lys Ser Ala Ala Ala Leu Asp
465 470 475 480

Ala Gln Ala Ala Arg Leu Ser Ala His Ile Ala Ala Tyr Pro Glu Gln
485 490 495

Gly Leu Gly Asp Val Ala Phe Ser Leu Val Ser Thr Arg Ser Pro Met
500 505 510

Glu His Arg Leu Ala Val Ala Ala Thr Ser Arg Glu Ala Leu Arg Ser
515 520 525

Ala Leu Glu Val Ala Ala Gln Gly Gln Thr Pro Ala Gly Ala Ala Arg
530 535 540

Gly Arg Ala Ala Ser Ser Pro Gly Lys Leu Ala Phe Leu Phe Ala Gly
545 550 555 560

Gln Gly Ala Gln Val Pro Gly Met Gly Arg Gly Leu Trp Glu Ala Trp
565 570 575

Pro Ala Phe Arg Glu Thr Phe Asp Arg Cys Val Thr Leu Phe Asp Arg
580 585 590

Glu Leu His Gln Pro Leu Cys Glu Val Met Trp Ala Glu Pro Gly Ser
595 600 605

Ser Arg Ser Ser Leu Leu Asp Gln Thr Ala Phe Thr Gln Pro Ala Leu
610 615 620

Phe Ala Leu Glu Tyr Ala Leu Ala Ala Leu Phe Arg Ser Trp Gly Val
625 630 635 640

Glu Pro Glu Leu Val Ala Gly His Ser Leu Gly Glu Leu Val Ala Ala
645 650 655

Cys Val Ala Gly Val Phe Ser Leu Glu Asp Ala Val Arg Leu Val Val
660 665 670

```
Ala Arg Gly Arg Leu Met Gln Ala Leu Pro Ala Gly Gly Ala Met Val
        675                 680                 685

Ser Ile Ala Ala Pro Glu Ala Asp Val Ala Ala Ala Val Ala Pro His
    690                 695                 700

Ala Ala Leu Val Ser Ile Ala Ala Val Asn Gly Pro Glu Gln Val Val
705                 710                 715                 720

Ile Ala Gly Ala Glu Lys Phe Val Gln Gln Ile Ala Ala Ala Phe Ala
                725                 730                 735

Ala Arg Gly Ala Arg Thr Lys Pro Leu His Val Ser His Ala Phe His
            740                 745                 750

Ser Pro Leu Met Asp Pro Met Leu Glu Ala Phe Arg Arg Val Thr Glu
        755                 760                 765

Ser Val Thr Tyr Arg Arg Pro Ser Ile Ala Leu Val Ser Asn Leu Ser
    770                 775                 780

Gly Lys Pro Cys Thr Asp Glu Val Ser Ala Pro Gly Tyr Trp Val Arg
785                 790                 795                 800

His Ala Arg Glu Ala Val Arg Phe Ala Asp Gly Val Lys Ala Leu His
                805                 810                 815

Ala Ala Gly Ala Gly Leu Phe Val Glu Val Gly Pro Lys Pro Thr Leu
            820                 825                 830

Leu Gly Leu Val Pro Ala Cys Leu Pro Asp Ala Arg Pro Val Leu Leu
        835                 840                 845

Pro Ala Ser Arg Ala Gly Arg Asp Glu Ala Ala Ser Ala Leu Glu Ala
    850                 855                 860

Leu Gly Gly Phe Trp Val Val Gly Gly Ser Val Thr Trp Ser Gly Val
865                 870                 875                 880

Phe Pro Ser Gly Gly Arg Arg Val Pro Leu Pro Thr Tyr Pro Trp Gln
                885                 890                 895

Arg Glu Arg Tyr Trp Ile Glu Ala Pro Val Asp Arg Glu Ala Asp Gly
            900                 905                 910

Thr Gly Arg Ala Arg Ala Gly Gly His Pro Leu Leu Gly Glu Val Phe
        915                 920                 925

Ser Val Ser Thr His Ala Gly Leu Arg Leu Trp Glu Thr Thr Leu Asp
    930                 935                 940

Arg Lys Arg Leu Pro Trp Leu Gly Glu His Arg Ala Gln Gly Glu Val
945                 950                 955                 960

Val Phe Pro Gly Ala Gly Tyr Leu Glu Met Ala Leu Ser Ser Gly Ala
                965                 970                 975

Glu Ile Leu Gly Asp Gly Pro Ile Gln Val Thr Asp Val Val Leu Ile
            980                 985                 990

Glu Thr Leu Thr Phe Ala Gly Asp Thr Ala Val Pro Val Gln Val Val
        995                 1000                1005

Thr Thr Glu Glu Arg Pro Gly Arg Leu Arg Phe Gln Val Ala Ser Arg
    1010                1015                1020
```

Glu Pro Gly Glu Arg Arg Ala Pro Phe Arg Ile His Ala Arg Gly Val
1025 1030 1035 1040

Leu Arg Arg Ile Gly Arg Val Glu Thr Pro Ala Arg Ser Asn Leu Ala
1045 1050 1055

Ala Leu Arg Ala Arg Leu His Ala Ala Val Pro Ala Ala Ala Ile Tyr
1060 1065 1070

Gly Ala Leu Ala Glu Met Gly Leu Gln Tyr Gly Pro Ala Leu Arg Gly
1075 1080 1085

Leu Ala Glu Leu Trp Arg Gly Glu Gly Glu Ala Leu Gly Arg Val Arg
1090 1095 1100

Leu Pro Glu Ala Ala Gly Ser Ala Thr Ala Tyr Gln Leu His Pro Val
1105 1110 1115 1120

Leu Leu Asp Ala Cys Val Gln Met Ile Val Gly Ala Phe Ala Asp Arg
1125 1130 1135

Asp Glu Ala Thr Pro Trp Ala Pro Val Glu Val Gly Ser Val Arg Leu
1140 1145 1150

Phe Gln Arg Ser Pro Gly Glu Leu Trp Cys His Ala Arg Val Val Ser
1155 1160 1165

Asp Gly Gln Gln Ala Ser Ser Arg Trp Ser Ala Asp Phe Glu Leu Met
1170 1175 1180

Asp Gly Thr Gly Ala Val Val Ala Glu Ile Ser Arg Leu Val Val Glu
1185 1190 1195 1200

Arg Leu Ala Ser Gly Val Arg Arg Arg Asp Ala Asp Asp Trp Phe Leu
1205 1210 1215

Glu Leu Asp Trp Glu Pro Ala Ala Leu Gly Gly Pro Lys Ile Thr Ala
1220 1225 1230

Gly Arg Trp Leu Leu Leu Gly Glu Gly Gly Gly Leu Gly Arg Ser Leu
1235 1240 1245

Cys Ser Ala Leu Lys Ala Ala Gly His Val Val Val His Ala Ala Gly
1250 1255 1260

Asp Asp Thr Ser Thr Ala Gly Met Arg Ala Leu Leu Ala Asn Ala Phe
1265 1270 1275 1280

Asp Gly Gln Ala Pro Thr Ala Val Val His Leu Ser Ser Leu Asp Gly
1285 1290 1295

Gly Gly Gln Leu Gly Pro Gly Leu Gly Ala Gln Gly Ala Leu Asp Ala
1300 1305 1310

Pro Arg Ser Pro Asp Val Asp Ala Asp Ala Leu Glu Ser Ala Leu Met
1315 1320 1325

Arg Gly Cys Asp Ser Val Leu Ser Leu Val Gln Ala Leu Val Gly Met
1330 1335 1340

Asp Leu Arg Asn Ala Pro Arg Leu Trp Leu Leu Thr Arg Gly Ala Gln
1345 1350 1355 1360

Ala Ala Ala Ala Gly Asp Val Ser Val Val Gln Ala Pro Leu Leu Gly

1365 1370 1375

Leu Gly Arg Thr Ile Ala Leu Glu His Ala Glu Leu Arg Cys Ile Ser
1380 1385 1390

Val Asp Leu Asp Pro Ala Glu Pro Glu Gly Glu Ala Asp Ala Leu Leu
1395 1400 1405

Ala Glu Leu Leu Ala Asp Asp Ala Glu Glu Glu Val Ala Leu Arg Gly
1410 1415 1420

Gly Asp Arg Leu Val Ala Arg Leu Val His Arg Leu Pro Asp Ala Gln
1425 1430 1435 1440

Arg Arg Glu Lys Val Glu Pro Ala Gly Asp Arg Pro Phe Arg Leu Glu
1445 1450 1455

Ile Asp Glu Pro Gly Ala Leu Asp Gln Leu Val Leu Arg Ala Thr Gly
1460 1465 1470

Arg Arg Ala Pro Gly Pro Gly Glu Val Glu Ile Ser Val Glu Ala Ala
1475 1480 1485

Gly Leu Asp Ser Ile Asp Ile Gln Leu Ala Leu Gly Val Ala Pro Asn
1490 1495 1500

Asp Leu Pro Gly Glu Glu Ile Glu Pro Leu Val Leu Gly Ser Glu Cys
1505 1510 1515 1520

Ala Gly Arg Ile Val Ala Val Gly Glu Gly Val Asn Gly Leu Val Val
1525 1530 1535

Gly Gln Pro Val Ile Ala Leu Ala Ala Gly Val Phe Ala Thr His Val
1540 1545 1550

Thr Thr Ser Ala Thr Leu Val Leu Pro Arg Pro Leu Gly Leu Ser Ala
1555 1560 1565

Thr Glu Ala Ala Ala Met Pro Leu Ala Tyr Leu Thr Ala Trp Tyr Ala
1570 1575 1580

Leu Asp Lys Val Ala His Leu Gln Ala Gly Glu Arg Val Leu Ile His
1585 1590 1595 1600

Ala Glu Ala Gly Gly Val Gly Leu Cys Ala Val Arg Trp Ala Gln Arg
1605 1610 1615

Val Gly Ala Glu Val Tyr Ala Thr Ala Asp Thr Pro Glu Asn Arg Ala
1620 1625 1630

Tyr Leu Glu Ser Leu Gly Val Arg Tyr Val Ser Asp Ser Arg Ser Gly
1635 1640 1645

Arg Phe Val Thr Asp Val His Ala Trp Thr Asp Gly Glu Gly Val Asp
1650 1655 1660

Val Val Leu Asp Ser Leu Ser Gly Glu Arg Ile Asp Lys Ser Leu Met
1665 1670 1675 1680

Val Leu Arg Ala Cys Gly Arg Leu Val Lys Leu Gly Arg Arg Asp Asp
1685 1690 1695

Cys Ala Asp Thr Gln Pro Gly Leu Pro Pro Leu Leu Arg Asn Phe Ser
1700 1705 1710

Phe Ser Gln Val Asp Leu Arg Gly Met Met Leu Asp Gln Pro Ala Arg
1715 1720 1725

Ile Arg Ala Leu Leu Asp Glu Leu Phe Gly Leu Val Ala Ala Gly Ala
1730 1735 1740

Ile Ser Pro Leu Gly Ser Gly Leu Arg Val Gly Gly Ser Leu Thr Pro
1745 1750 1755 1760

Pro Pro Val Glu Thr Phe Pro Ile Ser Arg Ala Ala Glu Ala Phe Arg
1765 1770 1775

Arg Met Ala Gln Gly Gln His Leu Gly Lys Leu Val Leu Thr Leu Asp
1780 1785 1790

Asp Pro Glu Val Arg Ile Arg Ala Pro Ala Glu Ser Ser Val Ala Val
1795 1800 1805

Arg Ala Asp Gly Thr Tyr Leu Val Thr Gly Gly Leu Gly Gly Leu Gly
1810 1815 1820

Leu Arg Val Ala Gly Trp Leu Ala Glu Arg Gly Ala Gly Gln Leu Val
1825 1830 1835 1840

Leu Val Gly Arg Ser Gly Ala Ala Ser Ala Glu Gln Arg Ala Ala Val
1845 1850 1855

Ala Ala Leu Glu Ala His Gly Ala Arg Val Thr Val Ala Lys Ala Asp
1860 1865 1870

Val Ala Asp Arg Ser Gln Ile Glu Arg Val Leu Arg Glu Val Thr Ala
1875 1880 1885

Ser Gly Met Pro Leu Arg Gly Val Val His Ala Ala Gly Leu Val Asp
1890 1895 1900

Asp Gly Leu Leu Met Gln Gln Thr Pro Ala Arg Phe Arg Thr Val Met
1905 1910 1915 1920

Gly Pro Lys Val Gln Gly Ala Leu His Leu His Thr Leu Thr Arg Glu
1925 1930 1935

Ala Pro Leu Ser Phe Phe Val Leu Tyr Ala Ser Ala Ala Gly Leu Phe
1940 1945 1950

Gly Ser Pro Gly Gln Gly Asn Tyr Ala Ala Ala Asn Ala Phe Leu Asp
1955 1960 1965

Ala Leu Ser His His Arg Arg Ala Gln Gly Leu Pro Ala Leu Ser Ile
1970 1975 1980

Asp Trp Gly Met Phe Thr Glu Val Gly Met Ala Val Ala Gln Glu Asn
1985 1990 1995 2000

Arg Gly Ala Arg Gln Ile Ser Arg Gly Met Arg Gly Ile Thr Pro Asp
2005 2010 2015

Glu Gly Leu Ser Ala Leu Ala Arg Leu Leu Glu Gly Asp Arg Val Gln
2020 2025 2030

Thr Gly Val Ile Pro Ile Thr Pro Arg Gln Trp Val Glu Phe Tyr Pro
2035 2040 2045

Ala Thr Ala Ala Ser Arg Arg Leu Ser Arg Leu Val Thr Thr Gln Arg
2050 2055 2060

Ala Val Ala Asp Arg Thr Ala Gly Asp Arg Asp Leu Leu Glu Gln Leu
2065 2070 2075 2080

Ala Ser Ala Glu Pro Ser Ala Arg Ala Gly Leu Leu Gln Asp Val Val
2085 2090 2095

Arg Val Gln Val Ser His Val Leu Arg Leu Pro Glu Asp Lys Ile Glu
2100 2105 2110

Val Asp Ala Pro Leu Ser Ser Met Gly Met Asp Ser Leu Met Ser Leu
2115 2120 2125

Glu Leu Arg Asn Arg Ile Glu Ala Ala Leu Gly Val Ala Ala Pro Ala
2130 2135 2140

Ala Leu Gly Trp Thr Tyr Pro Thr Val Ala Ala Ile Thr Arg Trp Leu
2145 2150 2155 2160

Leu Asp Asp Ala Leu Val Val Arg Leu Gly Gly Gly Ser Asp Thr Asp
2165 2170 2175

Glu Ser Thr Ala Ser Ala Gly Ser Phe Val His Val Leu Arg Phe Arg
2180 2185 2190

Pro Val Val Lys Pro Arg Ala Arg Leu Phe Cys Phe His Gly Ser Gly
2195 2200 2205

Gly Ser Pro Glu Gly Phe Arg Ser Trp Ser Glu Lys Ser Glu Trp Ser
2210 2215 2220

Asp Leu Glu Ile Val Ala Met Trp His Asp Arg Ser Leu Ala Ser Glu
2225 2230 2235 2240

Asp Ala Pro Gly Lys Lys Tyr Val Gln Glu Ala Ala Ser Leu Ile Gln
2245 2250 2255

His Tyr Ala Asp Ala Pro Phe Ala Leu Val Gly Phe Ser Leu Gly Val
2260 2265 2270

Arg Phe Val Met Gly Thr Ala Val Glu Leu Ala Ser Arg Ser Gly Ala
2275 2280 2285

Pro Ala Pro Leu Ala Val Phe Thr Leu Gly Gly Ser Leu Ile Ser Ser
2290 2295 2300

Ser Glu Ile Thr Pro Glu Met Glu Thr Asp Ile Ile Ala Lys Leu Phe
2305 2310 2315 2320

Phe Arg Asn Ala Ala Gly Phe Val Arg Ser Thr Gln Gln Val Gln Ala
2325 2330 2335

Asp Ala Arg Ala Asp Lys Val Ile Thr Asp Thr Met Val Ala Pro Ala
2340 2345 2350

Pro Gly Asp Ser Lys Glu Pro Pro Val Lys Ile Ala Val Pro Ile Val
2355 2360 2365

Ala Ile Ala Gly Ser Asp Asp Val Ile Val Pro Pro Ser Asp Val Gln
2370 2375 2380

Asp Leu Gln Ser Arg Thr Thr Glu Arg Phe Tyr Met His Leu Leu Pro
2385 2390 2395 2400

Gly Asp His Glu Phe Leu Val Asp Arg Gly Arg Glu Ile Met His Ile

```
                2405                2410                2415

Val Asp Ser His Leu Asn Pro Leu Leu Ala Ala Arg Thr Thr Ser Ser
            2420                2425                2430

Gly Pro Ala Phe Glu Ala Lys
        2435


&lt;210&gt; 8
&lt;211&gt; 419
&lt;212&gt; PRT
&lt;213&gt; Sorangium cellulosum

&lt;400&gt; 8
Met Thr Gln Glu Gln Ala Asn Gln Ser Glu Thr Lys Pro Ala Phe Asp
  1               5                  10                  15

Phe Lys Pro Phe Ala Pro Gly Tyr Ala Glu Asp Pro Phe Pro Ala Ile
             20                  25                  30

Glu Arg Leu Arg Glu Ala Thr Pro Ile Phe Tyr Trp Asp Glu Gly Arg
         35                  40                  45

Ser Trp Val Leu Thr Arg Tyr His Asp Val Ser Ala Val Phe Arg Asp
     50                  55                  60

Glu Arg Phe Ala Val Ser Arg Glu Glu Trp Glu Ser Ser Ala Glu Tyr
 65                  70                  75                  80

Ser Ser Ala Ile Pro Glu Leu Ser Asp Met Lys Lys Tyr Gly Leu Phe
                 85                  90                  95

Gly Leu Pro Pro Glu Asp His Ala Arg Val Arg Lys Leu Val Asn Pro
            100                 105                 110

Ser Phe Thr Ser Arg Ala Ile Asp Leu Leu Arg Ala Glu Ile Gln Arg
        115                 120                 125

Thr Val Asp Gln Leu Leu Asp Ala Arg Ser Gly Gln Glu Glu Phe Asp
    130                 135                 140

Val Val Arg Asp Tyr Ala Glu Gly Ile Pro Met Arg Ala Ile Ser Ala
145                 150                 155                 160

Leu Leu Lys Val Pro Ala Glu Cys Asp Glu Lys Phe Arg Arg Phe Gly
                165                 170                 175

Ser Ala Thr Ala Arg Ala Leu Gly Val Gly Leu Val Pro Gln Val Asp
            180                 185                 190

Glu Glu Thr Lys Thr Leu Val Ala Ser Val Thr Glu Gly Leu Ala Leu
        195                 200                 205

Leu His Asp Val Leu Asp Glu Arg Arg Arg Asn Pro Leu Glu Asn Asp
    210                 215                 220

Val Leu Thr Met Leu Leu Gln Ala Glu Ala Asp Gly Ser Arg Leu Ser
225                 230                 235                 240

Thr Lys Glu Leu Val Ala Leu Val Gly Ala Ile Ile Ala Ala Gly Thr
                245                 250                 255

Asp Thr Thr Ile Tyr Leu Ile Ala Phe Ala Val Leu Asn Leu Leu Arg
            260                 265                 270
```

Ser Pro Glu Ala Leu Glu Leu Val Lys Ala Glu Pro Gly Leu Met Arg
275 280 285

Asn Ala Leu Asp Glu Val Leu Arg Phe Asp Asn Ile Leu Arg Ile Gly
290 295 300

Thr Val Arg Phe Ala Arg Gln Asp Leu Glu Tyr Cys Gly Ala Ser Ile
305 310 315 320

Lys Lys Gly Glu Met Val Phe Leu Leu Ile Pro Ser Ala Leu Arg Asp
325 330 335

Gly Thr Val Phe Ser Arg Pro Asp Val Phe Asp Val Arg Arg Asp Thr
340 345 350

Gly Ala Ser Leu Ala Tyr Gly Arg Gly Pro His Val Cys Pro Gly Val
355 360 365

Ser Leu Ala Arg Leu Glu Ala Glu Ile Ala Val Gly Thr Ile Phe Arg
370 375 380

Arg Phe Pro Glu Met Lys Leu Lys Glu Thr Pro Val Phe Gly Tyr His
385 390 395 400

Pro Ala Phe Arg Asn Ile Glu Ser Leu Asn Val Ile Leu Lys Pro Ser
405 410 415

Lys Ala Gly

<210> 9
<211> 607
<212> PRT
<213> Sorangium cellulosum

<400> 9
Ala Ser Leu Asp Ala Leu Phe Ala Arg Ala Thr Ser Ala Arg Val Leu
1 5 10 15

Asp Asp Gly His Gly Arg Ala Thr Glu Arg His Val Leu Ala Glu Ala
20 25 30

Arg Gly Ile Glu Asp Leu Arg Ala Leu Arg Glu His Leu Arg Ile Gln
35 40 45

Glu Gly Gly Pro Ser Phe His Cys Met Cys Leu Gly Asp Leu Thr Val
50 55 60

Glu Leu Leu Ala His Asp Gln Pro Leu Ala Ser Ile Ser Phe His His
65 70 75 80

Ala Arg Ser Leu Arg His Pro Asp Trp Thr Ser Asp Ala Met Leu Val
85 90 95

Asp Gly Pro Ala Leu Val Arg Trp Leu Ala Ala Arg Gly Ala Pro Gly
100 105 110

Pro Leu Arg Glu Tyr Glu Glu Glu Arg Glu Arg Ala Arg Thr Ala Gln
115 120 125

Glu Ala Arg Arg Leu Trp Leu Ala Ala Ala Pro Pro Cys Phe Ala Pro
130 135 140

Asp Leu Pro Arg Phe Glu Asp Asp Ala Asn Gly Leu Pro Leu Gly Pro
145 150 155 160

Met Ser Pro Glu Val Ala Glu Ala Glu Arg Arg Leu Arg Ala Ser Tyr
165 170 175

Ala Thr Pro Glu Leu Ala Cys Ala Ala Leu Leu Ala Trp Leu Gly Thr
180 185 190

Gly Ala Gly Pro Trp Ser Gly Tyr Pro Ala Tyr Glu Met Leu Pro Glu
195 200 205

Asn Leu Leu Leu Gly Phe Gly Leu Pro Thr Ala Ile Ala Ala Ala Ser
210 215 220

Ala Pro Gly Thr Ser Glu Ala Ala Leu Arg Gly Ala Ala Arg Leu Phe
225 230 235 240

Ala Ser Trp Glu Val Val Ser Ser Lys Lys Ser Gln Leu Gly Asn Ile
245 250 255

Pro Glu Ala Leu Trp Glu Arg Leu Arg Thr Ile Val Arg Ala Met Gly
260 265 270

Asn Ala Asp Asn Leu Ser Arg Phe Glu Arg Ala Glu Ala Ile Ala Ala
275 280 285

Glu Val Arg Arg Leu Arg Ala Gln Pro Ala Pro Phe Ala Ala Gly Ala
290 295 300

Gly Leu Ala Val Ala Gly Val Ser Ser Ser Gly Arg Leu Ser Gly Leu
305 310 315 320

Val Thr Asp Gly Asp Ala Leu Tyr Ser Gly Asp Gly Asn Asp Ile Val
325 330 335

Met Phe Gln Pro Gly Arg Ile Ser Pro Val Val Leu Leu Ala Gly Thr
340 345 350

Asp Pro Phe Phe Glu Leu Ala Pro Pro Leu Ser Gln Met Leu Phe Val
355 360 365

Ala His Ala Asn Ala Gly Thr Ile Ser Lys Val Leu Thr Glu Gly Ser
370 375 380

Pro Leu Ile Val Met Ala Arg Asn Gln Ala Arg Pro Met Ser Leu Val
385 390 395 400

His Ala Arg Gly Phe Met Ala Trp Val Asn Gln Ala Met Val Pro Asp
405 410 415

Pro Glu Arg Gly Ala Pro Phe Val Val Gln Arg Ser Thr Ile Met Glu
420 425 430

Phe Glu His Pro Thr Pro Arg Cys Leu His Glu Pro Ala Gly Ser Ala
435 440 445

Phe Ser Leu Ala Cys Asp Glu Glu His Leu Tyr Trp Cys Glu Leu Ser
450 455 460

Ala Gly Arg Leu Glu Leu Trp Arg His Pro His His Arg Pro Gly Ala
465 470 475 480

Pro Ser Arg Phe Ala Tyr Leu Gly Glu His Pro Ile Ala Ala Thr Trp
485 490 495

```
Tyr Pro Ser Leu Thr Leu Asn Ala Thr His Val Leu Trp Ala Asp Pro
            500                 505                 510

Asp Arg Arg Ala Ile Leu Gly Val Asp Lys Arg Thr Gly Val Glu Pro
        515                 520                 525

Ile Val Leu Ala Glu Thr Arg His Pro Pro Ala His Val Val Ser Glu
    530                 535                 540

Asp Arg Asp Ile Phe Ala Leu Thr Gly Gln Pro Asp Ser Arg Asp Trp
545                 550                 555                 560

His Val Glu His Ile Arg Ser Gly Ala Ser Thr Val Val Ala Asp Tyr
                565                 570                 575

Gln Arg Gln Leu Trp Asp Arg Pro Asp Met Val Leu Asn Arg Arg Gly
            580                 585                 590

Leu Phe Phe Thr Thr Asn Asp Arg Ile Leu Thr Leu Ala Arg Ser
        595                 600                 605


<210> 10
<211> 423
<212> PRT
<213> Sorangium cellulosum

<400> 10
Met Gly Ala Leu Ile Ser Val Ala Ala Pro Gly Cys Ala Leu Gly Gly
  1               5                  10                  15

Ala Glu Glu Glu Gly Gln Pro Gly Gln Asp Ala Gly Ala Gly Ala Leu
            20                  25                  30

Ala Pro Ala Arg Glu Val Met Ala Ala Glu Val Ala Ala Gly Gln Met
        35                  40                  45

Pro Gly Ala Val Trp Leu Val Ala Arg Gly Asp Asp Val His Val Asp
    50                  55                  60

Ala Val Gly Val Thr Glu Leu Gly Gly Ser Ala Pro Met Arg Arg Asp
65                  70                  75                  80

Thr Ile Phe Arg Ile Ala Ser Met Thr Lys Ala Val Thr Ala Thr Ala
                85                  90                  95

Val Met Met Leu Val Glu Glu Gly Lys Leu Asp Leu Asp Ser Pro Val
            100                 105                 110

Asp Arg Trp Leu Pro Glu Leu Ala Asn Arg Lys Val Leu Ala Arg Ile
        115                 120                 125

Asp Gly Pro Ile Asp Glu Thr Val Pro Ala Glu Arg Pro Ile Thr Val
    130                 135                 140

Arg Asp Leu Met Thr Phe Thr Met Gly Phe Gly Ile Ser Phe Asp Ala
145                 150                 155                 160

Ser Ser Pro Ile Gln Arg Ala Ile Asp Glu Leu Gly Leu Val Asn Ala
                165                 170                 175

Gln Pro Val Pro Met Thr Pro His Gly Pro Asp Glu Trp Ile Arg Arg
            180                 185                 190
```

Leu Gly Thr Leu Pro Leu Met His Gln Pro Gly Ala Gln Trp Met Tyr
195 200 205

Asn Thr Gly Ser Leu Val Gln Gly Val Leu Val Gly Arg Ala Ala Asp
210 215 220

Gln Gly Phe Asp Ala Phe Val Arg Glu Arg Ile Leu Ala Pro Leu Gly
225 230 235 240

Met Arg Asp Thr Asp Phe His Val Pro Ala Asp Lys Leu Ala Arg Phe
245 250 255

Ala Gly Cys Gly Tyr Phe Thr Asp Glu Gln Thr Gly Glu Lys Thr Arg
260 265 270

Met Asp Arg Asp Gly Ala Glu Ser Ala Tyr Ala Ser Pro Pro Ala Phe
275 280 285

Pro Ser Gly Ala Ala Gly Leu Val Ser Thr Val Asp Asp Tyr Leu Leu
290 295 300

Phe Ala Arg Met Leu Met Asn Gly Gly Val His Glu Gly Arg Arg Leu
305 310 315 320

Leu Ser Ala Ala Ser Val Arg Glu Met Thr Ala Asp His Leu Thr Pro
325 330 335

Ala Gln Lys Ala Ala Ser Ser Phe Phe Pro Gly Phe Phe Glu Thr His
340 345 350

Gly Trp Gly Tyr Gly Met Ala Val Val Thr Ala Pro Asp Ala Val Ser
355 360 365

Glu Val Pro Gly Arg Tyr Gly Trp Asp Gly Gly Phe Gly Thr Ser Trp
370 375 380

Ile Asn Asp Pro Gly Arg Glu Leu Ile Gly Ile Val Met Thr Gln Ser
385 390 395 400

Ala Gly Phe Leu Phe Ser Gly Ala Leu Glu Arg Phe Trp Arg Ser Val
405 410 415

Tyr Val Ala Thr Glu Ser Ala
420

<210> 11
<211> 713
<212> PRT
<213> Sorangium cellulosum

<400> 11
Met His Gly Leu Thr Glu Arg Gln Val Leu Leu Ser Leu Val Thr Leu
1 5 10 15

Ala Leu Ile Leu Val Thr Ala Arg Ala Ser Gly Glu Leu Ala Arg Arg
20 25 30

Leu Arg Gln Pro Glu Val Leu Gly Glu Leu Phe Gly Gly Val Val Leu
35 40 45

Gly Pro Ser Val Val Gly Ala Leu Ala Pro Gly Phe His Arg Ala Leu
50 55 60

Phe Gln Glu Pro Ala Val Gly Val Val Leu Ser Gly Ile Ser Trp Ile

65 70 75 80

Gly Ala Leu Leu Leu Leu Leu Met Ala Gly Ile Glu Val Asp Val Gly
85 90 95

Ile Leu Arg Lys Glu Ala Arg Pro Gly Ala Leu Ser Ala Leu Gly Ala
100 105 110

Ile Ala Pro Pro Leu Ala Ala Gly Ala Ala Phe Ser Ala Leu Val Leu
115 120 125

Asp Arg Pro Leu Pro Ser Gly Leu Phe Leu Gly Ile Val Leu Ser Val
130 135 140

Thr Ala Val Ser Val Ile Ala Lys Val Leu Ile Glu Arg Glu Ser Met
145 150 155 160

Arg Arg Ser Tyr Ala Gln Val Thr Leu Ala Ala Gly Val Val Ser Glu
165 170 175

Val Ala Ala Trp Val Leu Val Ala Met Thr Ser Ser Ser Tyr Gly Ala
180 185 190

Ser Pro Ala Leu Ala Val Ala Arg Ser Ala Leu Leu Ala Ser Gly Phe
195 200 205

Leu Leu Phe Met Val Leu Val Gly Arg Arg Leu Thr His Leu Ala Met
210 215 220

Arg Trp Val Ala Asp Ala Thr Arg Val Ser Lys Gly Gln Val Ser Leu
225 230 235 240

Val Leu Val Leu Thr Phe Leu Ala Ala Ala Leu Thr Gln Arg Leu Gly
245 250 255

Leu His Pro Leu Leu Gly Ala Phe Ala Leu Gly Val Leu Leu Asn Ser
260 265 270

Ala Pro Arg Thr Asn Arg Pro Leu Leu Asp Gly Val Gln Thr Leu Val
275 280 285

Ala Gly Leu Phe Ala Pro Val Phe Phe Val Leu Ala Gly Met Arg Val
290 295 300

Asp Val Ser Gln Leu Arg Thr Pro Ala Ala Trp Gly Thr Val Ala Leu
305 310 315 320

Leu Leu Ala Thr Ala Thr Ala Ala Lys Val Val Pro Ala Ala Leu Gly
325 330 335

Ala Arg Leu Gly Gly Leu Arg Gly Ser Glu Ala Ala Leu Val Ala Val
340 345 350

Gly Leu Asn Met Lys Gly Gly Thr Asp Leu Ile Val Ala Ile Val Gly
355 360 365

Val Glu Leu Gly Leu Leu Ser Asn Glu Ala Tyr Thr Met Tyr Ala Val
370 375 380

Val Ala Leu Val Thr Val Thr Ala Ser Pro Ala Leu Leu Ile Trp Leu
385 390 395 400

Glu Lys Arg Ala Pro Pro Thr Gln Glu Glu Ser Ala Arg Leu Glu Arg
405 410 415

Glu Glu Ala Ala Arg Arg Ala Tyr Ile Pro Gly Val Glu Arg Ile Leu
420 425 430

Val Pro Ile Val Ala His Ala Leu Pro Gly Phe Ala Thr Asp Ile Val
435 440 445

Glu Ser Ile Val Ala Ser Lys Arg Lys Leu Gly Glu Thr Val Asp Ile
450 455 460

Thr Glu Leu Ser Val Glu Gln Gln Ala Pro Gly Pro Ser Arg Ala Ala
465 470 475 480

Gly Glu Ala Ser Arg Gly Leu Ala Arg Leu Gly Ala Arg Leu Arg Val
485 490 495

Gly Ile Trp Arg Gln Arg Arg Glu Leu Arg Gly Ser Ile Gln Ala Ile
500 505 510

Leu Arg Ala Ser Arg Asp His Asp Leu Leu Val Ile Gly Ala Arg Ser
515 520 525

Pro Ala Arg Ala Arg Gly Met Ser Phe Gly Arg Leu Gln Asp Ala Ile
530 535 540

Val Gln Arg Ala Glu Ser Asn Val Leu Val Val Val Gly Asp Pro Pro
545 550 555 560

Ala Ala Glu Arg Ala Ser Ala Arg Arg Ile Leu Val Pro Ile Ile Gly
565 570 575

Leu Glu Tyr Ser Phe Ala Ala Ala Asp Leu Ala Ala His Val Ala Leu
580 585 590

Ala Trp Asp Ala Glu Leu Val Leu Leu Ser Ser Ala Gln Thr Asp Pro
595 600 605

Gly Ala Val Val Trp Arg Asp Arg Glu Pro Ser Arg Val Arg Ala Val
610 615 620

Ala Arg Ser Val Val Asp Glu Ala Val Phe Arg Gly Arg Arg Leu Gly
625 630 635 640

Val Arg Val Ser Ser Arg Val His Val Gly Ala His Pro Ser Asp Glu
645 650 655

Ile Thr Arg Glu Leu Ala Arg Ala Pro Tyr Asp Leu Leu Val Leu Gly
660 665 670

Cys Tyr Asp His Gly Pro Leu Gly Arg Leu Tyr Leu Gly Ser Thr Val
675 680 685

Glu Ser Val Val Val Arg Ser Arg Val Pro Val Ala Leu Leu Val Ala
690 695 700

His Gly Gly Thr Arg Glu Gln Val Arg
705 710

<210> 12
<211> 126
<212> PRT
<213> Sorangium cellulosum

<400> 12
Met Asp Lys Pro Ile Gly Arg Thr Arg Cys Ala Ile Ala Glu Gly Tyr

```
 1               5                   10                  15

Ile Pro Gly Gly Ser Asn Gly Pro Glu Pro Gln Met Thr Ser His Glu
            20                  25                  30

Thr Ala Cys Leu Leu Asn Ala Ser Asp Arg Asp Ala Gln Val Ala Ile
        35                  40                  45

Thr Val Tyr Phe Ser Asp Arg Asp Pro Ala Gly Pro Tyr Arg Val Thr
    50                  55                  60

Val Pro Ala Arg Arg Thr Arg His Val Arg Phe Asn Asp Leu Thr Glu
65                  70                  75                  80

Pro Glu Pro Ile Pro Arg Asp Thr Asp Tyr Ala Ser Val Ile Glu Ser
                85                  90                  95

Asp Ala Pro Ile Val Val Gln His Thr Arg Leu Asp Ser Arg Gln Ala
            100                 105                 110

Glu Asn Ala Leu Leu Ser Thr Ile Ala Tyr Thr Asp Arg Glu
        115                 120                 125


<210> 13
<211> 149
<212> PRT
<213> Sorangium cellulosum

<400> 13
Met Lys His Val Asp Thr Gly Arg Arg Phe Gly Arg Arg Ile Gly His
 1               5                   10                  15

Thr Leu Gly Leu Leu Ala Ser Met Ala Leu Ala Gly Cys Gly Gly Pro
            20                  25                  30

Ser Glu Lys Thr Val Gln Gly Thr Arg Leu Ala Pro Gly Ala Asp Ala
        35                  40                  45

Arg Val Thr Ala Asp Val Asp Pro Asp Ala Ala Thr Thr Arg Leu Ala
    50                  55                  60

Val Asp Val Val His Leu Ser Pro Pro Glu Arg Leu Glu Ala Gly Ser
65                  70                  75                  80

Glu Arg Phe Val Val Trp Gln Arg Pro Ser Pro Glu Ser Pro Trp Arg
                85                  90                  95

Arg Val Gly Val Leu Asp Tyr Asn Ala Asp Ser Arg Arg Gly Lys Leu
            100                 105                 110

Ala Glu Thr Thr Val Pro Tyr Ala Asn Phe Glu Leu Leu Ile Thr Ala
        115                 120                 125

Glu Lys Gln Ser Ser Pro Gln Ser Pro Ser Ser Ala Ala Val Ile Gly
    130                 135                 140

Pro Thr Ser Val Gly
145


<210> 14
<211> 184
<212> PRT
<213> Sorangium cellulosum
```

<400> 14
Val Thr Ser Glu Glu Val Pro Gly Ala Ala Leu Gly Ala Gln Ser Ser
1 5 10 15

Leu Val Arg Ala Gln His Ala Ala Arg His Val Arg Pro Cys Thr Arg
20 25 30

Ala Glu Glu Pro Pro Ala Leu Met His Gly Leu Thr Glu Arg Gln Val
35 40 45

Leu Leu Ser Leu Val Ala Leu Ala Leu Val Leu Leu Thr Ala Arg Ala
50 55 60

Phe Gly Glu Leu Ala Arg Arg Leu Arg Gln Pro Glu Val Leu Gly Glu
65 70 75 80

Leu Phe Gly Gly Val Val Leu Gly Pro Ser Val Val Gly Ala Leu Ala
85 90 95

Pro Gly Phe His Arg Val Leu Phe Gln Asp Pro Ala Val Gly Val Val
100 105 110

Leu Ser Gly Ile Ser Trp Ile Gly Ala Leu Val Leu Leu Leu Met Ala
115 120 125

Gly Ile Glu Val Asp Val Ser Ile Leu Arg Lys Glu Ala Arg Pro Gly
130 135 140

Ala Leu Ser Ala Leu Gly Ala Ile Ala Pro Pro Leu Arg Thr Pro Gly
145 150 155 160

Pro Leu Val Gln Arg Met Gln Gly Ala Phe Thr Trp Asp Leu Asp Val
165 170 175

Ser Pro Arg Arg Ser Ala Gln Ala
180

<210> 15
<211> 145
<212> PRT
<213> Sorangium cellulosum

<400> 15
Val Asn Ala Pro Cys Met Arg Cys Thr Ser Gly Pro Gly Val Arg Ser
1 5 10 15

Gly Gly Ala Ile Ala Pro Ser Ala Glu Ser Ala Pro Gly Arg Ala Ser
20 25 30

Leu Arg Arg Met Leu Thr Ser Thr Ser Ile Pro Ala Met Ser Ser Arg
35 40 45

Thr Ser Ala Pro Ile Gln Glu Met Pro Glu Ser Thr Thr Pro Thr Ala
50 55 60

Gly Ser Trp Lys Arg Thr Arg Trp Asn Pro Gly Ala Ser Ala Pro Thr
65 70 75 80

Thr Asp Gly Pro Ser Thr Thr Pro Pro Lys Ser Ser Pro Ser Thr Ser
85 90 95

Gly Trp Arg Ser Arg Arg Ala Ser Ser Pro Lys Ala Arg Ala Val Arg
100 105 110

Arg Thr Ser Ala Arg Ala Thr Ser Glu Ser Arg Thr Cys Arg Ser Val
115 120 125

Arg Pro Cys Ile Arg Ala Gly Gly Ser Ser Ala Arg Val Gln Gly Arg
130 135 140

Thr
145

<210> 16
<211> 185
<212> PRT
<213> Sorangium cellulosum

<400> 16
Val Leu Ala Pro Pro Ala Asp Ile Arg Pro Pro Ala Ala Ala Gln Leu
1 5 10 15

Glu Pro Asp Ser Pro Asp Asp Glu Ala Asp Glu Ala Asp Glu Ala Leu
20 25 30

Arg Pro Phe Arg Asp Ala Ile Ala Ala Tyr Ser Glu Ala Val Arg Trp
35 40 45

Ala Glu Ala Ala Gln Arg Pro Arg Leu Glu Ser Leu Val Arg Leu Ala
50 55 60

Ile Val Arg Leu Gly Lys Ala Leu Asp Lys Val Pro Phe Ala His Thr
65 70 75 80

Thr Ala Gly Val Ser Gln Ile Ala Gly Arg Leu Gln Asn Asp Ala Val
85 90 95

Trp Phe Asp Val Ala Ala Arg Tyr Ala Ser Phe Arg Ala Ala Thr Glu
100 105 110

His Ala Leu Arg Asp Ala Ala Ser Ala Met Glu Ala Leu Ala Ala Gly
115 120 125

Pro Tyr Arg Gly Ser Ser Arg Val Ser Ala Ala Val Gly Glu Phe Arg
130 135 140

Gly Glu Ala Ala Arg Leu His Pro Ala Asp Arg Val Pro Ala Ser Asp
145 150 155 160

Gln Gln Ile Leu Thr Ala Leu Arg Ala Ala Glu Arg Ala Leu Ile Ala
165 170 175

Leu Tyr Thr Ala Phe Ala Arg Glu Glu
180 185

<210> 17
<211> 146
<212> PRT
<213> Sorangium cellulosum

<400> 17
Met Ala Asp Ala Ala Ser Arg Ser Ala Cys Ser Val Ala Ala Arg Lys
1 5 10 15

Leu Ala Tyr Arg Ala Ala Thr Ser Asn Gln Thr Ala Ser Phe Trp Ser
20 25 30

Leu Pro Ala Ile Trp Glu Thr Pro Ala Val Val Cys Ala Lys Gly Thr
35 40 45

Leu Ser Ser Ala Leu Pro Ser Arg Thr Ile Ala Ser Arg Thr Arg Leu
50 55 60

Ser Ser Arg Gly Arg Cys Ala Ala Ser Ala His Arg Thr Ala Ser Glu
65 70 75 80

Tyr Ala Ala Ile Ala Ser Arg Asn Gly Arg Ser Ala Ser Ser Ala Ser
85 90 95

Ser Ala Ser Ser Ser Gly Glu Ser Gly Ser Ser Trp Ala Ala Ala Gly
100 105 110

Gly Arg Met Ser Ala Gly Gly Ala Ser Thr Gly Glu Val Tyr Glu Gln
115 120 125

Ala Pro Arg Leu Arg Leu Ala Gln Ser Val Ala Ala Arg Arg Arg Asp
130 135 140

Pro Thr
145

<210> 18
<211> 288
<212> PRT
<213> Sorangium cellulosum

<400> 18
Val Thr Val Ser Ser Met Pro Arg Ser Trp Ser Ser Arg Val Arg Thr
1 5 10 15

Val Val Thr Ala Leu Gly Cys Ala Arg Arg Leu Ser Gly Ser Ile Ser
20 25 30

Arg Leu Arg Arg His Pro Glu Ala Gly Arg Ala Pro Arg Ser Arg Leu
35 40 45

Arg Ala Trp Arg Arg Leu Pro Gln His Ile Ser Ser Pro Trp Arg His
50 55 60

Leu Pro Pro Gly Ala Arg Val Gly Thr Ser Cys Pro Ala Asp Arg Arg
65 70 75 80

Ile Leu Pro Ser His Arg Thr Ala Asp Leu Gly Thr Ser Gly Gly Thr
85 90 95

Leu Val Ala Arg Met Ser Gly His Val Ala Arg Asn Pro His Ala Ala
100 105 110

Val Leu Val Gly Asp Gly Ser Ala Arg Gly Arg Arg Arg Leu Ser Asn
115 120 125

Arg Arg Ala Glu Arg Arg Val Ser Asp Val Thr Cys Arg Glu Gly Gly
130 135 140

Glu Ala Met Gln Lys Ile Ala Gly Lys Leu Val Val Gly Leu Ile Ser
145 150 155 160

Val Ser Gly Met Ser Leu Leu Ala Ala Cys Gly Gly Glu Lys Arg Ser
165 170 175

Gly Gly Glu Ala Gln Thr Pro Gly Gly Ala Gln Gly Glu Ala Pro Val
180 185 190

Pro Val Gly Ser Ala Val Asp Ser Ile Val Ala Ala Arg Cys Asp Arg
195 200 205

Glu Ala Arg Cys Asn Asn Ile Gly Gln Asp Arg Glu Tyr Ser Ser Lys
210 215 220

Asp Ala Cys Ser Asn Lys Ile Arg Ser Glu Trp Arg Asp Glu Leu Thr
225 230 235 240

Phe Gly Glu Cys Pro Gly Gly Ile Asp Ala Lys Gln Leu Asn Glu Cys
245 250 255

Leu Glu Gly Ile Arg Asn Glu Gly Cys Gly Asn Pro Phe Asp Thr Leu
260 265 270

Gly Arg Val Val Ala Cys Arg Ser Ser Asp Leu Cys Arg Asp Ala Arg
275 280 285

<210> 19
<211> 288
<212> PRT
<213> Sorangium cellulosum

<400> 19
Val Thr Val Ser Ser Met Pro Arg Ser Trp Ser Ser Arg Val Arg Thr
1 5 10 15

Val Val Thr Ala Leu Gly Cys Ala Arg Arg Leu Ser Gly Ser Ile Ser
20 25 30

Arg Leu Arg Arg His Pro Glu Ala Gly Arg Ala Pro Arg Ser Arg Leu
35 40 45

Arg Ala Trp Arg Arg Leu Pro Gln His Ile Ser Ser Pro Trp Arg His
50 55 60

Leu Pro Pro Gly Ala Arg Val Gly Thr Ser Cys Pro Ala Asp Arg Arg
65 70 75 80

Ile Leu Pro Ser His Arg Thr Ala Asp Leu Gly Thr Ser Gly Gly Thr
85 90 95

Leu Val Ala Arg Met Ser Gly His Val Ala Arg Asn Pro His Ala Ala
100 105 110

Val Leu Val Gly Asp Gly Ser Ala Arg Gly Arg Arg Arg Leu Ser Asn
115 120 125

Arg Arg Ala Glu Arg Arg Val Ser Asp Val Thr Cys Arg Glu Gly Gly
130 135 140

Glu Ala Met Gln Lys Ile Ala Gly Lys Leu Val Val Gly Leu Ile Ser
145 150 155 160

Val Ser Gly Met Ser Leu Leu Ala Ala Cys Gly Gly Glu Lys Arg Ser
165 170 175

Gly Gly Glu Ala Gln Thr Pro Gly Gly Ala Gln Gly Glu Ala Pro Val

180 185 190

Pro Val Gly Ser Ala Val Asp Ser Ile Val Ala Ala Arg Cys Asp Arg
195 200 205

Glu Ala Arg Cys Asn Asn Ile Gly Gln Asp Arg Glu Tyr Ser Ser Lys
210 215 220

Asp Ala Cys Ser Asn Lys Ile Arg Ser Glu Trp Arg Asp Glu Leu Thr
225 230 235 240

Phe Gly Glu Cys Pro Gly Gly Ile Asp Ala Lys Gln Leu Asn Glu Cys
245 250 255

Leu Glu Gly Ile Arg Asn Glu Gly Cys Gly Asn Pro Phe Asp Thr Leu
260 265 270

Gly Arg Val Val Ala Cys Arg Ser Ser Asp Leu Cys Arg Asp Ala Arg
275 280 285

<210> 20
<211> 155
<212> PRT
<213> Sorangium cellulosum

<400> 20
Met Asp Pro Arg Ala Arg Arg Glu Lys Arg Pro Ser Leu Leu Asp Ser
1 5 10 15

Arg Gly Arg Gln Pro Lys Arg Ser Gln Gln Gly Gly His Met Glu Lys
20 25 30

Pro Ile Gly Arg Thr Arg Trp Ala Ile Ala Glu Gly Tyr Ile Pro Gly
35 40 45

Arg Ser Asn Gly Pro Glu Pro Gln Met Thr Ser His Glu Thr Ala Cys
50 55 60

Leu Leu Asn Ala Ser Asp Arg Asp Ala Gln Val Ala Ile Thr Val Tyr
65 70 75 80

Phe Ser Asp Arg Asp Pro Ala Gly Pro Tyr Arg Val Thr Val Pro Ala
85 90 95

Arg Arg Thr Arg His Val Arg Phe Asn Asp Leu Thr Glu Pro Glu Pro
100 105 110

Ile Pro Arg Asp Thr Asp Tyr Ala Ser Val Ile Glu Ser Asp Val Pro
115 120 125

Ile Val Val Gln His Thr Arg Leu Asp Ser Arg Gln Ala Glu Asn Ala
130 135 140

Leu Ile Ser Thr Ile Ala Tyr Thr Asp Arg Glu
145 150 155

<210> 21
<211> 156
<212> PRT
<213> Sorangium cellulosum

<400> 21
Val Arg Arg Ser Arg Trp Gln Met Lys His Val Asp Thr Gly Arg Arg
1   5   10   15

Val Gly Arg Arg Ile Gly Leu Thr Leu Gly Leu Leu Ala Ser Met Ala
            20   25   30

Leu Ala Gly Cys Gly Gly Pro Ser Glu Lys Ile Val Gln Gly Thr Arg
        35   40   45

Leu Ala Pro Gly Ala Asp Ala His Val Ala Ala Asp Val Asp Pro Asp
    50   55   60

Ala Ala Thr Thr Arg Leu Ala Val Asp Val Val His Leu Ser Pro Pro
65   70   75   80

Glu Arg Ile Glu Ala Gly Ser Glu Arg Phe Val Val Trp Gln Arg Pro
                85   90   95

Ser Ser Glu Ser Pro Trp Gln Arg Val Gly Val Leu Asp Tyr Asn Ala
            100   105   110

Ala Ser Arg Arg Gly Lys Leu Ala Glu Thr Thr Val Pro His Ala Asn
        115   120   125

Phe Glu Leu Leu Ile Thr Val Glu Lys Gln Ser Ser Pro Gln Ser Pro
    130   135   140

Ser Ser Ala Ala Val Ile Gly Pro Thr Ser Val Gly
145   150   155

<210> 22
<211> 305
<212> PRT
<213> Sorangium cellulosum

<400> 22
Met Glu Lys Glu Ser Arg Ile Ala Ile Tyr Gly Ala Ile Ala Ala Asn
1   5   10   15

Val Ala Ile Ala Ala Val Lys Phe Ile Ala Ala Ala Val Thr Gly Ser
            20   25   30

Ser Ala Met Leu Ser Glu Gly Val His Ser Leu Val Asp Thr Ala Asp
        35   40   45

Gly Leu Leu Leu Leu Leu Gly Lys His Arg Ser Ala Arg Pro Pro Asp
    50   55   60

Ala Glu His Pro Phe Gly His Gly Lys Glu Leu Tyr Phe Trp Thr Leu
65   70   75   80

Ile Val Ala Ile Met Ile Phe Ala Ala Gly Gly Gly Val Ser Ile Tyr
                85   90   95

Glu Gly Ile Leu His Leu Leu His Pro Arg Gln Ile Glu Asp Pro Thr
            100   105   110

Trp Asn Tyr Val Val Leu Gly Ala Ala Ala Val Phe Glu Gly Thr Ser
        115   120   125

Leu Ile Ile Ser Ile His Glu Phe Lys Lys Lys Asp Gly Gln Gly Tyr
    130   135   140

Leu Ala Ala Met Arg Ser Ser Lys Asp Pro Thr Thr Phe Thr Ile Val
145 150 155 160

Leu Glu Asp Ser Ala Ala Leu Ala Gly Leu Thr Ile Ala Phe Leu Gly
165 170 175

Val Trp Leu Gly His Arg Leu Gly Asn Pro Tyr Leu Asp Gly Ala Ala
180 185 190

Ser Ile Gly Ile Gly Leu Val Leu Ala Ala Val Ala Val Phe Leu Ala
195 200 205

Ser Gln Ser Arg Gly Leu Leu Val Gly Glu Ser Ala Asp Arg Glu Leu
210 215 220

Leu Ala Ala Ile Arg Ala Leu Ala Ser Ala Asp Pro Gly Val Ser Ala
225 230 235 240

Val Gly Arg Pro Leu Thr Met His Phe Gly Pro His Glu Val Leu Val
245 250 255

Val Leu Arg Ile Glu Phe Asp Ala Ala Leu Thr Ala Ser Gly Val Ala
260 265 270

Glu Ala Ile Glu Arg Ile Glu Thr Arg Ile Arg Ser Glu Arg Pro Asp
275 280 285

Val Lys His Ile Tyr Val Glu Ala Arg Ser Leu His Gln Arg Ala Arg
290 295 300

Ala
305

<210> 23
<211> 135
<212> PRT
<213> Sorangium cellulosum

<400> 23
Val Gln Thr Ser Ser Phe Asp Ala Arg Tyr Ala Gly Cys Lys Ser Ser
1 5 10 15

Arg Arg Ile Ala Arg Ser Gly Ser Ala Gly Ala Arg Ala Gly Arg Ala
20 25 30

His Glu Gly Ala Ala Ser Ala Gly Phe Glu Gly Gly Asp Val Met Arg
35 40 45

Lys Ala Arg Ala His Gly Ala Met Leu Gly Gly Arg Asp Asp Gly Trp
50 55 60

Arg Arg Gly Leu Pro Gly Ala Gly Ala Leu Arg Ala Ala Leu Gln Arg
65 70 75 80

Gly Arg Ser Arg Asp Leu Ala Arg Arg Arg Leu Ile Ala Ser Val Ser
85 90 95

Leu Ala Gly Gly Ala Ser Met Ala Val Val Ser Leu Phe Gln Leu Gly
100 105 110

Ile Ile Glu Arg Leu Pro Asp Pro Pro Leu Pro Gly Phe Asp Ser Ala
115 120 125

```
Lys Val Thr Ser Ser Asp Ile
    130                 135


<210> 24
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: universal
      reverse primer

<400> 24
ggaaacagct atgaccatg                                              19

<210> 25
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: universal
      forward primer

<400> 25
gtaaaacgac ggccagt                                                17

<210> 26
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer
      NH24 end "B"

<400> 26
gtgactggcg cctggaatct gcatgagc                                    28

<210> 27
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer NH2
      end "A"

<400> 27
agcgggagct tgctagacat tctgtttc                                    28

<210> 28
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer NH2
      end "B"

<400> 28
gacgcgcctc gggcagcgcc ccaa                                        24

<210> 29
```

<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer
pEPO15-NH6 end "B"

<400> 29
caccgaagcg tcgatctggt ccatc 25

<210> 30
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer
pEPO15H2.7 end "A"

<400> 30
cggtcagatc gacgacgggc tttcc 25